The Regulation of Medicinal Products: an Analysis of the Impact on Pharmaceutical Innovation, Consumer Safety and Legal Redress

Volume One

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Abstract

The adverse consequences of the use of thalidomide in the 1950s and 1960s by pregnant women, instigated law reform in the United Kingdom and Europe, in relation to product liability and the regulation of medicinal products. In this Thesis, it is suggested that a legislative framework should balance three elements: consumer safety, legal redress and pharmaceutical innovation.

Chapter Three examines the development of the legislative framework in the United Kingdom following thalidomide and considers the impact of the Medicines Act 1968, the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 and the Consumer Protection Act 1987, together with European legislation, on medicinal products. This Chapter also examines the role of regulatory bodies such as the Medicines Control Agency, the Committee on Safety of Medicines, the European Agency for the Evaluation of Medicinal Products and the Committee on Proprietary Medicinal Products.

Chapter Four analyses the three above mentioned elements and, in particular, discusses: the centralised and decentralised licensing procedures; the definition of "relevant medicinal product"; the regulation of homeopathic products, herbal products and medical devices; conflicts of interest; transparency of licensing procedures; the legal status of medicinal products; promotion by the pharmaceutical industry; information supplied to patients; pharmacovigilance; and the development risks defence.

The Author concluded that the legislative framework had struck an appropriate (albeit imperfect) balance between the elements of pharmaceutical innovation, consumer safety and legal redress. The Author further concluded that issues such as patents, prescribing errors and legal aid, which are outwith the control of the Medicines Act 1968 and the Consumer Protection Act 1987, impact on the balance of these three elements. In the future, the Author suggested that research should be conducted in areas such as transparency of regulatory action, the regulation of herbal products, and the improvement of prescribing and dispensing practices.

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Abbreviations

ABPI	Association of the British Pharmaceutical Industry
ABRHP	Advisory Board on the Registration of Homeopathic Medicinal Products
ADR	Adverse Drug Reaction
BMA	British Medical Association
BNF	British National Formulary
BPC	British Pharmacopoeia Commission
CDSM	Committee on Dental and Surgical Materials
CMR	Centre for Medicines Research
CPMP	Committee on Proprietary Medicinal Products
CRM	Committee on Review of Medicines
CSD	Committee on Safety of Drugs
CSM	Committee on Safety of Medicines
DHSS	Department of Health and Social Security
EFPIA	European Federation of Pharmaceutical Industries' Association
EMEA	European Agency for the Evaluation of Medicinal Products
FDA	Food and Drug Administration
MCA	Medicines Control Agency
MMR	Measles, Mumps and Rubella vaccines
NCC	National Consumer Council
NCE	New Chemical Entity
NSAID	Non-Steroidal Anti-Inflammatory Drug
OHE	Office of Health Economics
OTC	Over The Counter
PAGB	Proprietary Association of Great Britain
PMCPA	Prescription Medicines Code of Practice Authority
SPC	Sumary of Product Characteristics

Chapter One

Therapeutic Roses and their Thorns*

1.1 The Legacy of Thalidomide

> " The most harrowing association of pharmaceutical medicine and the law was the experience of thalidomide, which led to a global appreciation of the necessity for drug regulation on a much firmer basis than had ever previously been considered." [1]

In 1957, thalidomide was marketed in Germany by the pharmaceutical company, Chemie Grünenthal.[2] One year later, Distillers Co. (Biochemicals) Ltd manufactured and marketed thalidomide in the United Kingdom, under the trade name Distaval. It was used as a sedative and was popular because it was inexpensive and

> " It had prompt action, gave a natural deep sleep with no hangover, and appeared to be innocent and safe." [3]

In 1959, reports of an unusual birth defect, phocomelia, started to appear in German medical journals.[4] In 1961, Lenz, in Germany, and McBride, in Australia, linked further similar reports to women who had taken thalidomide while they were pregnant.[5] On 2 December 1961, thalidomide was withdrawn in the United Kingdom.[6] Worldwide more than ten thousand children were born with thalidomide-induced injuries[7]; four hundred and fifty were born in the United Kingdom.[8] The disabilities caused by thalidomide included: limb deficiencies; ear anomalies; eye

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* "Unfortunately there are no therapeutic roses without their thorns", Dunlop quoted in Penn (1979) p300.

[1]Goldberg, A., "Pharmaceutical Medicine and the Law: An Historical Perspective", in Goldberg and Dodds-Smith (1991), p10.

[2]See Teff and Munro (1976), Stewart, R.B. (1985) and Hodges and Appelbe (1987b) for additional background information and a detailed account of the events surrounding thalidomide.

[3]Hodges and Appelbe (1987b) p151.

[4]Stewart, R.B. (1985) p20.

[5]Ibid pp21-23.

[6]Teff and Munro (1976) pxi. Thalidomide was withdrawn in Germany on 28 November 1961. [Stewart, R.B. op. cit. p23].

[7]Stewart op. cit. p23 The countries involved included: Germany, Japan, Australia, Canada, Belgium, the Netherlands, Brazil, Egypt, Israel, Peru, Spain, Sweden, Switzerland and the United States.

[8]Quibell (1981).

defects; heart defects; bowel anomalies; urological defects; gynaecological defects; dwarfism; spinal anomalies; obesity; epilepsy; autism; and facial palsy.[9]

The struggle for compensation for the "thalidomide children" has been well-documented by Teff and Munro in their book, "Thalidomide: The Legal Aftermath".10 After a protracted campaign in The Sunday Times and other newspapers, a settlement was reached and, in 1973, Distillers set up a trust fund to provide financial support to these children.

Surprisingly, more than thirty years after its withdrawal, media, public and medical attention is still focused on thalidomide. To illustrate this point, a search on the Internet (using the Alta Vista search engine) in October 1997, listed more than 2,000 articles worldwide which concerned thalidomide; 600 were in English. These articles originated from universities, medical journals, regulatory bodies and patients' groups, and covered such wide-ranging topics as the historical background to thalidomide, its current uses, new clinical trials being undertaken and the supply of thalidomide by "AIDS buyers'" clubs. A similar search on the newspaper database NEXIS listed several hundred newspaper articles written within recent years on the subject of thalidomide.

In the UK, thalidomide has been the subject of much media interest, following, for example, the hunger strikes staged in 1994 by several members of the Thalidomide Action Group to highlight the perceived failure of the Thalidomide Trust to meet the long-term financial needs of the "thalidomide children".[11] Following this campaign, Guinness (who had bought over Distillers) and the

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[9]Ibid. Smithells (1973) also examines the disabilities of the "thalidomide children".
[10]Op cit.
[11]Christie (1994).

Government agreed to pay additional sums of money into the trust fund.[12] Also, there have been allegations reported recently in the media, that the adverse effects of thalidomide may have been inherited by the children of the original thalidomide victims and a test case is being brought by the father of one of these children.[13] Thalidomide has also been the subject of several television programmes.[14] Yorkshire Television broadcast a programme entitled "Thalidomide: the drug that came back". This programme examined the misuse of thalidomide in Brazil by pregnant women, where it is used legitimately in the treatment of lepra reaction, and it reported that 21 children had been born with limb deformities.[15]

> " How could it be that a drug whose effects are so well known could still be allowed to maim innocent victims today." [16]

Interestingly, thalidomide has been used beneficially, not only in the treatment of lepra reaction, but also in the treatment of many other diseases including Behçet's syndrome, actinic prurigo, AIDS-related oral ulcers and cachexia, rheumatoid arthritis and Graft-Versus-Host disease.[17]

> " Many would be surprised to learn that thalidomide, the notorious teratogen of the early 1960s, has not disappeared from therapeutic use. In fact, an extensive body of literature clearly demonstrates that the drug has extraordinary value in the treatment of several debilitating diseases refractory to conventional therapy." [18]

It has also been suggested that thalidomide may be useful potentially in the treatment of multiple sclerosis, Crohn's disease and Alzheimer's disease.[19] It has been reported

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[12]See "Guinness to pay thalidomide victims extra £2.5m a year", The Scotsman, 4 May 1995 and "Thalidomide campaign bears fruit at last", The Herald, 7 June 1996.

[13]"Test case over inherited thalidomide deformity", The Scotsman, 14 May 1997. See also "Threat to the victims' children", The Herald, 7 September 1995 and "New fears voiced on thalidomide", The Herald, 11 August 1997.

[14]Including World in Action, "Victims of their Success" and Focal Point, "Thalidomide: A price still to pay?". Both programmes focused on the inadequacy of the compensation arrangements, and were broadcast in 1993/94.

[15]Pharmaceutical Journal (1993w). See also Rocha (1994).

[16]Part of the First Tuesday series and broadcast on 1 June 1993.

[17]For further information, see Lancet (1985d), Kaitin (1988), Günzler (1992), Sherman and Strauss (1986), Randall (1990), Jakeman and Smith (1994), Carmichael and Knight (1994) and Higgins and Bradbeer (1994).

[18]Kaitin (1988) p207.

[19]Thompson (1995).

recently, that the Food and Drug Administration (FDA), may license thalidomide for treatment of lepra reaction in the USA.[20]

As expected, the use of thalidomide is extremely controversial and has been the subject of debate in the medical press, with views ranging from:

> " Is it not time that all the remaining supplies of thalidomide tablets were consigned to the flames?" [21]

to:

> " The fact that there are many countries in which the regulation of medicines supply is so imperfect as to allow the over-the-counter sale of teratogens is no reason to deny ourselves the benefits of their use under a proper level of supervision. It is for the offending countries to demonstrate their commitment to the health of their citizens by regulating the supply of medicines properly." [22]

and:

> " It is highly unlikely that thalidomide will ever be widely distributed or achieve anything more than investigational status. None the less, it would be unfortunate if patients who respond favourably to thalidomide after failing to respond to conventional therapy are denied access to it. The time has come for the medical establishment, national drug agencies and public to reconsider the unjustified blanket stigmatisation of this drug." [23]

In May 1994, the controversy over the use of thalidomide culminated in the Committee on Safety of Medicines issuing a set of guidelines.[24]

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[20] Pharmaceutical Journal (1997a).
[21] Hawkins (1994).
[22] Harris (1993).
[23] Kaitin (1988) p208.
[24] " • Thalidomide should only be used by specialists in severe and disabling conditions where all other treatments have been tried and failed.
• No woman who is pregnant or may become pregnant should be treated.
• Each patient must be able to understand the risk of thalidomide use and be able to comply with the safety instructions. They must receive a detailed patient information leaflet and sign a consent form.
• Careful records must be kept. The doctor and pharmacist must ensure that the container is labelled "thalidomide". "thalidomide causes serious damage to babies if taken by women during pregnancy" and "this drug must not be shared with anyone else".
• Peripheral neuropathy is a recognised side-effect which may be reversed by stopping treatment. Regular review is required to ensure early diagnosis."
CSM and MCA (1994b). Thalidomide does not have a product licence but is used only on a "named patient" basis.

The focus of the media on the negative legacies of thalidomide has overshadowed the positive aspects of this medicinal product. As well as being a useful medical treatment in certain diseases, thalidomide is widely regarded as being responsible for law reform in the United Kingdom,[25] the European Community[26] and many other countries.[27]

1.2 Proposal for an Analysis of the Legislative Framework introduced following Thalidomide

The recent re-examination of thalidomide in the general media and medical press regarding the controversy surrounding its use, suggested to the Author that the legislative framework introduced following thalidomide should be reviewed in order to discuss current safeguards and analyse whether or not a catastrophe such as that caused by thalidomide could happen again. However, "success" cannot be gauged with reference to the prevention of another thalidomide tragedy. It is argued by the

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25" Its repercussions and profound influence on the law are gradually emerging. A major consequence has been the tightening up of regulations governing the testing, advertising and production of drugs and medicines throughout the world. More recently, the sheer delay in meeting the claims of the parents and children has also highlighted certain technical shortcomings of our legal system, more particularly in the way in which it handles negligence cases and the rules constituting the law of contempt. Precisely because of its catastrophic dimensions, the thalidomide affair is proving to be a catalyst for changing the law in both of these spheres."
Teff and Munro (1976). Other countries also responded to thalidomide; Kelsey (1988) documented the U.S. reaction and commented that the Food, Drug and Cosmetic Act 1938 had been "adequate to prevent the marketing of thalidomide in this country, but the episode did serve to call attention to the inadequacies of this Act and hastened, if not ensured, its amendment in October 1962."

26" Of all industrial sectors, it is perhaps the pharmaceutical industry which is subject to the greatest level of regulation and control by the public authorities.
Following the thalidomide tragedy, all the developed countries adopted increasingly sophisticated systems for the authorization of the marketing of medicinal products designed to ensure that before they are placed on the market, medicines are proved to be of good quality, safe for patients and efficacious for the therapeutic indications proposed. In addition, the manufacture of medicinal products, their labelling and the provision of information to patients and doctors about medicines are all subject to strict controls. The need for such legislation is recognized by all concerned, not least by the pharmaceutical industry itself.
In addition, the pharmaceutical industry is subject to a variety of economic regulations which are designed to ensure that medicines are made available to patients at reasonable prices and to contain the overall level of expenditure on pharmaceutical products within the framework of the national health insurance systems.
Ever since the adoption of the first pharmaceutical directive in 1965, it has been recognized that the Community institutions also have an important role to play in the pharmaceutical sector."
Commission of the European Communities (1989a) p1.

Author that "success" is dependent on the achievement of a subtle balance between science and law. This is discussed by Dunlop:

> " Though science does not always lend itself to legislative or regulatory manipulation, modern drugs are such potent weapons that there is a general consensus that the sole responsibility for their production and use can no longer be left entirely to the manufacturer or prescriber. Yet it is difficult to know how far Government should attempt to control their production and prescription without undue interference with the advance of scientific therapeutics, the well-being of the pharmaceutical industry, and the cherished freedom of the doctor, dentist or veterinary surgeon to prescribe as he thinks best. Inadequate regulation may prejudice public safety but excessive regulation can also be prejudicial in stultifying innovation and delaying the introduction of valuable remedies. The thoughtful legislator must direct his efforts between these two extremes and protect the public from inadequately tested and dangerous drugs, but at the same time permit an orderly progress of research, development and marketing by the pharmaceutical industry. The operation of controls must be efficient, economical, and expeditious for otherwise the public are denied new and useful drugs." [28]

It is further argued by the Author of this thesis that the "thoughtful legislator", described by Dunlop, must also direct his efforts towards developing a system of legal redress which compensates those injured by medicinal products but does not, through the threat of legal action, unduly prejudice the introduction of new products.

A legislative framework must balance three elements: pharmaceutical innovation, consumer safety and legal redress. Pharmaceutical innovation refers to the ability of the pharmaceutical industry to develop new products; consumer safety refers to the protection of consumers from the adverse effects of medicinal products; and legal redress refers to the ability of consumers to obtain compensation for injuries caused by medicinal products. The aim of this thesis is to examine the hypothesis that the legislative framework has not struck an appropriate balance between the elements of pharmaceutical innovation, consumer safety and legal redress. For the purposes of

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[27]For example, Clark (1989) p11 mentions the role of thalidomide as a catalyst in the development of the law

this thesis, the "legislative framework" refers not only to the legislation implemented in the UK and Europe following thalidomide,[29] but also regulations relating to medicinal products which have been introduced, including self-regulatory codes, such as, the Code of Practice for the Pharmaceutical Industry (which is discussed in Chapter Four).[30]

In the remainder of this Chapter, the Author will set out the general background and introduce the concepts of pharmaceutical innovation, consumer safety and legal redress.

1.3 Pharmaceutical Innovation

> " Research and development is the single most important area of effort for research-based companies. Only through this can the momentum of advances in health care be maintained and new medicines developed to the highest possible standards." [31]

It was reported in the Annual Review of the Association of the British Pharmaceutical Industry (ABPI) for 1996 that, since 1992, expenditure on pharmaceutical research and development had risen by nearly 500 per cent to more than £2 billion a year and that there were 200 new molecules in clinical development in the UK.32 The Review also summarised the areas of research in which pharmaceutical companies are currently working, which include asthma, cancer,

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relating to product liability.
[28]Dunlop in Davies (1991) p. ix.
[29] For example, the Medicines Act 1968, the Consumer Protection Act 1987 and Directive 65/65/EEC on the regulation of medicinal products. This thesis does not discuss the common law as this has been discussed in detail elsewhere. For example, Clark (1989).
[30] p250.
[31]ABPI (1994) p32
[32] ABPI (1997) p29.

drug-resistant bacterial infections, cardiovascular disease, multiple sclerosis, Alzheimer's disease, arthritis, hepatitis and schizophrenia. [33]

A report from the Centre for Medicines Research (CMR) noted that research and development expenditure in thirteen countries with a research and development-based pharmaceutical industry had increased from US $5bn in 1981 to an estimated US$26.5bn in 1993.[34] However, the annual output of new chemical entities (NCEs) had decreased from 66 in 1981 to 40 in 1993. The CMR viewed this decrease as "significant" and stated that it

> " raises questions about the ability of the pharmaceutical industry to continue to commit such high investment to researching and developing NCEs." [35]

According to the ABPI, it takes 10 to 12 years to develop a new medicinal product and this costs more than £200 million.[36] Appendix I outlines the stages in the discovery and development of a new medicinal product.

Pharmaceutical innovation results not only in medical benefits but also economic growth. A report from the Office of Health Economics (founded by the ABPI) concluded that the value of the pharmaceutical industry to the UK economy is approximately £2 billion per year.[37]

Part I of Chapter Four of this thesis will examine the effect of the legislative framework on pharmaceutical innovation.[38]

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[33]Ibid pp29-30.
[34]Lumley (1995). The countries involved in the survey were: United Kingdom, USA, Japan, Germany, France, Switzerland, Italy, Sweden, Canada, Belgium, Spain, The Netherlands and Denmark. The UK spent £1.64bn on research and development in 1993.
[35]Ibid p1.
[36]ABPI (1991c) and (1996) p34. See also Collee (1992) for further information on the development of new medicinal products.
[37]Office of Health Economics (1995).
[38] p153.

1.4 Consumer Safety

The media has an increasingly influential role with regard to influencing public opinion on issues concerning medicinal products. Griffin has suggested that the media focuses on three aspects of medicinal products:

> " 1. Stories about wonder drugs that a regulatory authority refuses to license, thereby denying the public amazingly efficacious remedies.
> 2. Hazard stories relating to widely used and commercially successful products where the basic claim is that the regulatory authorities are failing to protect the public.
> 3. An outcry that when an obsolete drug is removed from the market, perhaps after a long and honourable history; the regulatory authority acted tardily in not dealing with the matter years earlier." [39]

Inman has commented that the development of "trial by television" is of particular concern:

> " Confidence in drug treatment is being seriously eroded by the activities of the media and I believe it is very important to establish a base-line so that the safety of other new drugs may be assessed more realistically in the future. There seems to be a real danger that the media rather than the medical community may determine what treatment you may offer to your patients in the future..." [40]

In recent years, television programmes have featured items on Prozac[41], steroids[42], Septrin[43], dental amalgam[44] and Femodene[45]. This year, the BBC television programme "Watchdog" has featured many items on Lariam and silicone breast implants; "World in Action has featured an item on the treatment of headlice with

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[39]D'Arcy and Griffin (1986) p3.
[40]Drug Surveillance Research Unit (1983) p14.
[41]"Everyman", 14 August 1994. See Lader (1994) for details.
[42]"Here and Now", 23 November 1994. See Pharmaceutical Journal (1994a) for details.
[43]"News at Ten", 31 October 1994. See Pharmaceutical Journal (1994b) for details.
[44]"Panorama", 11 July 1994. See Mjör (1994)for details.
[45]"World in Action", 10 July 1995. See Pharmaceutical Journal (1995b) for details.

Derbac M.[46]; and there has been great debate in the general media and the medical press on Gulf War Syndrome.[47]

However, it is suggested that the loss of public confidence in the pharmaceutical industry and the safety of medicinal products referred to by Inman, began much earlier with the controversy surrounding thalidomide. Smith commented:

> " The past 20 years have seen a gradual change in public attitudes to drugs, medicines and vaccines from adulation to profound suspicion. In the immediate postwar years antibiotics dramatically cut deaths from tuberculosis, pneumonia, and eventually almost all bacterial diseases, while vaccines virtually eliminated poliomyelitis and controlled other virus infections. For a while drugs - and the pharmaceutical industry - rated high in public esteem and modern therapeutics was seen as one of the most worthwhile technical advances of the current century. Disenchantment began with the catastrophic epidemic of deformities from thalidomide, compounded by the sorry tale of calculating pragmatism that emerged as the victims sought compensation. Next, critics such as Ivan Illich began to point to the failure of modern medicine to cure or even alleviate many of the non-infectious, chronic disorders; and Thomas McKeown argued that most of the drop in mortality this century in Western countries was attributable to improvements in hygiene and not to any advances in clinical medicine. During the 1970s, a series of reports linked first cyclamates and later saccharine with bladder cancer in rats; oral contraceptives were shown to cause thromboembolic disease and liver tumours; breast cancer was attributed to reserpine; and addiction to tranquillisers was portrayed as a major public health problem." [48]

Since thalidomide, there have been a number of well-publicised withdrawals of medicinal products and medical devices, and reports of serious adverse drug reactions: practolol (Eraldin) and ocular damage;[49] Reye's syndrome and the use of

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[46] Pharm J (1997b).
[47] David et al (1997), Lancet (1997a), (1997b), Lancet (1996a), (1996b) and (1996c).
[48] Smith, T. (1980c) p1410. Public opinion of the pharmaceutical industry in the United States has deteriorated to the extent that the American Pharmaceutical Manufacturers' Association has allegedly paid a public relations consultant $5 to $7 million to "improve the industry's image".
" The industry has acquired a very negative image, one that combines the view of it as greedy beyond all avarice, with the even more damaging idea that it is thoroughly unscrupulous, puts profits before patient welfare and has no objection to endangering patients in order to increase profits." [Schwartz (1992a)]
[49] CSM (1975a).

aspirin by children;[50] benoxaprofen (Opren) and liver damage;[51] the Dalkon Shield and infertility;[52] pertussis vaccine and encephalopathy;[53] Diethylstilboestrol (DES) and vaginal adenocarcinoma;[54] benzodiazepines and dependence;[55] Björk-Shiley heart valves and strut fracture;[56] iophendylate (Myodil) and arachnoiditis;[57] MMR vaccines and meningitis;[58] triazolam (Halcion) and psychiatric adverse reactions;[59] co-trimoxazole (Septrin) and fatalities,[60] ; oral contraceptives and thromboembolism.[61]; and terfenadine and cardiac arrhythmia.[62]

In 1996, the Committee on Safety of Medicines (CSM) received 17,191 reports of suspected adverse reactions to medicinal products.[63] The CSM received these reports from doctors, dentists and H.M. coroners under the voluntary Yellow Card Scheme, and from pharmaceutical companies as a condition of their product licences.[64] This scheme has been in operation since 1964 and reports were originally sent to the Committee on Safety of Drugs (CSD).

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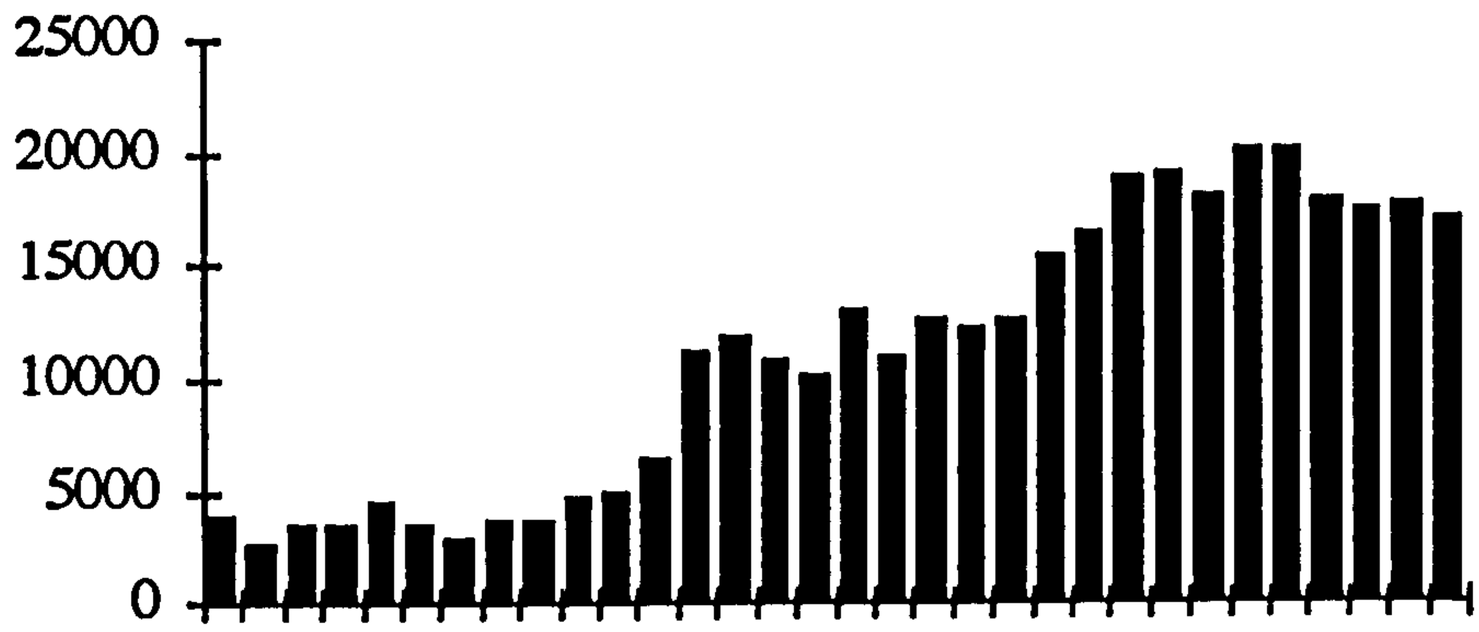
[50]CSM (1986a).
[51]CSM (1982a).
[52]Dyer (1990a).
[53]Brahams (1993).
[54]CSM (1973b).
[55]CSM (1988a).
[56]CSM (1990d).
[57]Pharmaceutical Journal (1992bbb).
[58]Pharmaceutical Journal (1992ff).
[59]CSM (1991b).
[60]Pharmaceutical Journal (1995a).
[61]Pharmaceutical Journal (1995b).
[62] CSM (1997a)
[63]Medicines Commission et al (1997) p22.
[64]Ibid.

Table 1 Adverse Reactions reported to the CSD and CSM (1965 - 1996).[65]



As can be seen, the number of suspected adverse reactions has increased over the years, but decreased in 1993, 1994, 1995 and 1996. The CSM expressed its concern over this decrease in their 1996 annual report and stated that the Committee would be "taking steps during 1997 to attempt to reverse this trend".[66] As from 1 April 1997, community pharmacists in certain areas and all hospital pharmacists started to report adverse reactions to the CSM.[67]

It is widely acknowledged by the CSM that adverse reactions are under-reported and the percentage actually reported could be as low as 13.5%.[68] A number of studies have attempted to estimate the true incidence of adverse reactions caused by medicinal products.

- Adverse drug reactions (defined as unintended effects of substances used in the prevention, diagnosis, or treatment of disease) are common. They are responsible

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[65]1965 was the first full year of operation of the scheme. These figures are taken from the annual reports of the CSD and CSM.
[66] Medicines Commission et al (1997) p23.
[67] Pharm J (1997c)
[68]Lumley et al (1986). This under-reporting will be discussed in relation to pharmacovigilance in Chapter Four.

> for 3-5% of hospital admissions, occur in 10-20% of hospital inpatients, and have recently been reported in 40% of patients receiving drugs in general practice." [69]

The 1980 report of the chief Medical Officer of the Department of Health and Social Security stated that about 100,000 people each year experience some "ill-effects" from medicinal products.[70] D'Arcy reviewed 42 international studies, from 1964 to 1984, relating to the incidence of adverse drug reactions during hospitalisation or attributable to hospital admission. Adverse reactions occurred in 0.66% to 36% of the patients studied.[71] Medawar gave three possible estimates of the incidence of adverse reactions per year in the UK: 47,000 serious adverse reactions and 2,500 deaths, or; 180,000 adverse reactions, or; 240,000 hospitalisations resulting wholly or largely from medicinal products.[72] There may be disagreement over the actual incidence of adverse reactions, but it is clear that there are risks, as well as benefits, involved in taking medicinal products.

> " Those who say that nothing but the complete safety of drugs will suffice demand the impossible: a drug without any side effects is probably an ineffective one. The public who require progress must be prepared for some risk: it has always accepted the not inconsiderable risks of surgery to which some modern drugs are equivalent in efficacy. While shuddering at a death rate of, say, one in 40,000 patients dying as a result of taking a usually valuable remedy [...] we are much more complacent about the far greater dangers of cigarette smoking, alcoholism or road accidents." [73]

Chapter Four of this thesis will examine the effect of the legislative framework on consumer safety.[74]

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[69]Rawlins (1981) p974.
[70]Pharmaceutical Journal (1982u).
[71]D'Arcy in D'Arcy and Griffin (1986) pp30-33.
[72]Medawar (1992a) p3. These estimates are disputed by the Association of the British Pharmaceutical Industry. See SCRIP (1992xx).
[73]Dunlop in Davies (1991) pvii.
[74] p166.

1.5 Legal Redress

In recent years, there has been an increase in the number of product liability cases involving medicinal products. For example, the litigation concerning benzodiazepines involved 13,000 claimants and was the largest ever multi-party action in the United Kingdom.[75] The legal journal "Product Liability International" had a regular feature called "Report Worldwide". This feature had a medical column which gave details on recalls, serious adverse reactions and developments in product liability actions from around the world involving medicinal products, medical devices and miscellaneous "medical" products. This journal has now amalgamated with another journal "Liability, Risk & Insurance", but issues involving these products continue to be reported. Appendix II lists the products mentioned in "Product Liability International" and "Liability, Risks & Insurance" in the period 1990 to 1997, states whether there was potential (i.e. a report of an adverse reaction of product recall) or actual legal action, names the country or countries involved, and gives the reference of the issue of journal where the report originally appeared.

In total, 138 medicinal products have been mentioned in the "Report Worldwide" column; 59 of these products involved actual or potential legal action in the United Kingdom. It can be seen from Appendix II that a diverse range of products has been mentioned in this column, including: aspirin, blood, x-ray equipment, benzodiazepines, breast implants, oral contraceptives, tampons and vaccines.

In 1994, the Journal of the Law Society of Scotland started to publish details of "matters which may give rise to claims", in a column called "Multiple Claims".[76]

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[75]Legal Aid Board (1994).
[76]Journal of the Law Society of Scotland (1994a).

Previously details of such claims appeared in the Law Society's Council Report.[77] A combination of twenty four medicinal products and medical devices have been mentioned in the "Multiple Claims" column and these are listed in Table 2.

Table 2 *Medicinal Products and Medical Devices mentioned in the "Multiple Claims" column of the Journal of the Law Society of Scotland (1994 - 1997)*[78]

- Co-proxamol. [July 1995]
- Cordarone X. [April 1994]
- Corticosteroids. [January 1996]
- Depo-Provera. [May 1995]
- Disposable contact lenses. [April 1994]
- Femodene. [March 1994]
- Hormone replacement therapy. [July 1995]
- Human growth hormone. [June 1994 and January 1997]
- Larium [March 1996]
- Losec [March 1996]
- Measles, mumps and rubella vaccine. [February 1995]
- Minocin. [May 1996]
- Myodil. [January 1996]
- Norplant contraceptive implants. [December 1995]
- Novopen Needles [April 1996]
- Oxazepam. [March 1995]
- Pacemakers. [February 1995 and February 1996]
- Radiotherapy. [April 1994]
- Radio frequency induced endometrial ablation. [June 1995]
- Septrin. [April 1994]
- Seroxat. [January 1995]
- Silicone breast implants. [April 1994 and October 1994]
- Smallpox vaccine. [March 1994]
- Zinnat. [March 1995]

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[77]The 1993 Council Report mentioned diethylstilboestrol (DES), Manoplax, whooping cough vaccine, Doxeplin, exposure to mercury in dental practice; Carbendazim and, hepatitis C and blood transfusion. Ibid.
[78] See entry in the bibliography under "Journal of the Law Society of Scotland".

This Table together with Appendix II illustrate, from a product liability perspective, the level of "interest" and/or activity of legal practitioners in actual or potential litigation concerning these types of product.

Very few product liability cases involving medicinal products have been resolved by court action; most have been decided by out-of-court settlements. Court cases have involved pertussis (whooping cough) vaccine,[79] smallpox vaccine,[80] neomycin,[81] benzodiazepines,[82] Primodos (a hormonal pregnancy test),[83] iophendylate (Myodil),[84] Factor VIII and HIV[85], benoxaprofen (Opren)[86] and human growth hormone.[87] However, the majority of these reported cases involved decisions relating to preliminary procedural issues such as the granting of legal aid or acquiring access to medical documents. Only the cases relating to pertussis

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[79]*R v Secretary of State for Social Services ex parte Loveday*, [1983] unreported (QBD); *R v Vaccine Damage Tribunal ex parte Loveday*, [1984] unreported (QBD); *Re Loveday's Judicial Review Application*, [1985] unreported (CA); *Loveday and others v Renton*, [1985] unreported (CA); *Loveday v Renton and another*, [1987], unreported, (CA); *Loveday v Renton and another*, [1988], unreported) (QBD); *Loveday v Renton and another* (No.2), [1992] 3 All ER 184; *R v Legal Aid Board ex p S*, [1992] unreported (QBD); *R v The Legal Aid Board ex p Shephard*, [1993] unreported (CA); *DHSS v Kinnear and others*, [1984] unreported (QBD); *R v Legal Aid Area No.8 (Northern) Appeal Committee, ex p Angell and others*, [1990] unreported (QBD); *Lesley Montgomery v Lothian Health Board and Secretary of State* [1989] unreported (Outer House); *Lesley Montgomery v Lothian Health Board and Another*, [1990] unreported (Inner House); *John Bonthrone and Another v Right Honourable Bruce Millan MP and Others*, [1985] unreported (Outer House); *Bonthrone v Secretary of State for Scotland*, [1987] SLT 34.

[80]*Ross v Secretary of State for Scotland* [1990] SLT 13.

[81]*Mann v Wellcome Foundation Limited and Others*; *Close v Wellcome Foundation Limited & Others*, [1989], unreported (QBD).

[82]*McInally v John Wyeth & Brother Ltd.*, [1991], unreported (Outer House); *McInally v John Wyeth & Brother Ltd.*, Outer House, [1992] SLT 344; *AB and others v John Wyeth & Brother Ltd and another*, [January 1991] unreported (QBD); *AB and others v John Wyeth & Brother Limited and another*, [May 1991] unreported (QBD); *AB and others v John Wyeth & Brother Ltd and others*, [1992] unreported (CA); *AB and others v John Wyeth & Brother Ltd and others*, [1992] unreported (QBD); *AB and others v John Wyeth & Brother Ltd and others*, [1993] unreported (CA); *Mohammed Nur v John Wyeth & Brother Ltd*, [1993] unreported (CA).

[83]*Hudd and Others v Schering Chemicals Ltd* [1980] unreported (CA) and, *H and another v Schering Chemicals Ltd*, [1983] 1 All ER 849.

[84]*Newman v Hounslow & Spelthorne Health Authority*, [1985], unreported, (QBD) and, *Chrzanowska v Glaxo Laboratories Ltd*, [1990] unreported (QBD).

[85]*Re HIV Haemophiliac Litigation*, [1990] unreported (CA).

[86]*Walker v Eli Lilly & Company and Others*, [1986] unreported (QBD); *Davies v Eli Lilly & Co and Others* [1986] unreported (QBD); *Pozzi v Eli Lilly & Company and Others* [1986] unreported (QBD); *Baker v Eli Lilly & Co and Others* [1986] unreported (QBD); *Davies v Eli Lilly & Co and Others* [May 1987] unreported (QBD); *Davies v Eli Lilly & Co and Others* [July 1987] unreported (QBD); *Davies v Eli Lilly & Co and Others*, [1987] 1 All ER 801 (CA); *Davies (Joseph Owen) v Eli Lilly & Co and others*, [1987] 3 All ER 94 (CA); *Davies v Eli Lilly*, [1988] unreported (QBD); *Beal v Eli Lilly & Co and Others* [1988] unreported (QBD); *R v The Legal Aid Area Committee No. 10 (East Midlands Area) ex parte McKenna*, [1989] unreported (QBD); *Nash and others v Eli Lilly & Company and others*, [1991] unreported (QBD); *Nash and others v Eli :Lilly & Co and others*, *Berger and others v Eli Lilly & Co and others*, [1993] 4 All ER 383.

[87]Dyer (1996).

vaccine, neomycin and human growth hormone have addressed the issue of whether the medicinal product concerned was responsible for an alleged injury. As yet there are no reported cases where action has been taken under the Consumer Protection Act 1987. However, it has been reported recently that an English firm of solicitors, Shoosmiths & Harrison of Reading, is bringing an action under the 1987 Act against Schering Healthcare, on behalf of a client who allegedly suffered adverse reactions associated with the oral contraceptive, Femodene.[88]

The numbers of actual/potential product liability cases involving medicinal products suggested to the Author that this may be an illustration of a failing in the legislative framework from the perspective that consumers were experiencing safety problems with certain medicinal products. Also, the fact that that there has been no action taken under the Consumer Protection Act 1987 suggested to the Author that there could be a problem with the system by which consumers sought legal redress.

Chapter Four of this thesis will examine the effect of the legislative framework on the ability of consumers to seek legal redress.[89]

1.6 Review of Issues to be Examined in this Thesis

Earlier in this Chapter,[90] the Author proposed that a legislative framework must balance three elements: pharmaceutical innovation, consumer safety and legal redress. The aim of this thesis is to examine the hypothesis that the legislative framework has not struck an appropriate balance between these three elements.

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[88] Pearson (1997).
[89] p281.
[90] p7.

The examination of this hypothesis is both interesting and important because the legislative framework in the UK, which comprises both national and European legislative provisions, was significantly amended on 1 January 1995 by The Medicines for Human Use (Marketing Authorizations etc.) Regulations 1994. These Regulations introduced a completely new basis for the licensing of medicinal products which will be discussed in later Chapters Three and Four.[91] The examination of this hypothesis comes at a time when there has not been much opportunity for other authors to comment on this new framework.

In Chapter Two, "Methods and Materials", the Author will discuss the research methodology of this thesis and the types of materials which were deemed necessary for a full examination of the above hypothesis. This will include reference to relevant organisations, bibliographic indexes, the Internet, legislative and regulatory sources, and publications.

In Chapter Three, "The Development of the Legislative Framework following Thalidomide", the Author will discuss: the historical background to the Consumer Protection Act 1987, the Medicines Act 1968 and European legislation relating to medicinal products; the role of the Committee on Safety of Drugs; the role of the Medicines Control Agency, Medicines Commission and expert advisory committees; the introduction of the Medicines for Human Use (Marketing Authorizations etc.) Regulations 1994; and the role of the European Agency for the Evaluation of Medicinal Products and the Committee for Proprietary Medicinal Products.

In Chapter Four, "An Analysis of Current Practice under the Legislative Framework as it Affects Pharmaceutical Innovation, Consumer Safety and Legal Redress", the Author will analyse the elements of the hypothesis and discuss the following issues: licensing times; homeopathic medicinal products; herbal products;

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[91] For example, p134.

medical devices; conflicts of interest; changes in the legal status of medicinal products; the promotion of medicinal products; information supplied to patients; pharmacovigilance; and the development risks defence.

In Chapter Five, "A Summary of Conclusions and Recommendations", the Author will summarise the issues discussed in this thesis and examine their effect on the hypothesis.

Chapter Two

Methods and Materials

2.1 Research Strategy

2.1.1 Introduction

The aim of this thesis is to analyse the effect of the legislative framework on consumer safety, pharmaceutical innovation and legal redress. To this end, the Author had to gather a diverse range of materials relating to medicinal products which included legislation, regulations, guidelines, leaflets, books and articles from a variety of medical, scientific and legal sources.

The investigation of these sources involved a full analysis of material at the interface of medicine, science and law. Although the analysis of these sources was conducted from the Author's legal perspective, the Author placed as much emphasis on the medical and scientific sources as the legal sources. Indeed, later in this Chapter,[92] the Author discusses the fact that medico-legal issues were reported more extensively and to a higher standard in medical and scientific journals rather than in legal journals. It is suggested by the Author that this approach of treating these medical, scientific and legal sources as being of equal importance and as interacting with one another, was the only means by which this thesis could have been properly researched. If these sources had been looked at in isolation or from the perspective of being of unequal importance then the Author would not have been fully aware of the extent of the legislative framework and the manner in which it operated in practice. For example, to appreciate why certain statutory instruments were introduced, the Author realised that medical and scientific materials which outlined

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[92] p49.

the problems in practice encountered by the operation of the licensing framework and which the statutory instrument was designed to solve, had to be examined.

This Chapter discusses the many ways in which materials at this interface were analysed. These include contacting people with a specialist knowledge in this area, using medical, scientific and legal bibliographic indexes, referring to legal, medical and scientific journals and books, contacting legal, medical and scientific organisations and using legal, medical and scientific websites on the Internet.

2.1.2 Initial Ideas

At the outset of the Author's research, Professor John Midgley (Supervisor, Department of Pharmaceutical Sciences) suggested that a useful way of obtaining ideas and information for this thesis would be to contact people with specialist knowledge in this area. He compiled a list of experts from the pharmaceutical industry, Medicines Control Agency, Committee on Safety of Medicines, Committee on the Review of Medicines, Association of the British Pharmaceutical Industry, Royal Pharmaceutical Society of Great Britain and several research organisations. It was also decided to contact representatives from consumer organisations. Each of the experts and representatives was sent a draft proposal of the thesis entitled "Medicinal Products: An Analysis of Current Regulation and Legal Remedies", with the following introduction:

> " It has been alleged that the regulatory measures controlling the quality, safety and efficacy of medicinal products fail to protect the consumer from injury and, also, that the available legal remedies do not afford adequate legal redress, despite the introduction of a system of strict liability by the Consumer Protection Act 1987. However, it has also been argued that the mass of current regulation inhibits the research and development of new products, and delays their introduction to the market."

Also included was an outline of the proposed chapters and their contents. Table 3 lists the individuals contacted and the positions they held at that time; symbols next to each name indicate whether contact was made by personal visit (✈), correspondence (✉) or telephone conversation (☎). The majority of personal visits occurred in May and June 1990; the correspondence and telephone discussions continued until December 1992.

Table 3 Experts contacted (1990 - 1992).

Dr P. Adams ☎	Product Licence Applications Section, Medicines Control Agency
Dr G.E. Appelbe ✈	Head of Law Department, Royal Pharmaceutical Society of Great Britain
Professor A.W. Asscher ✈	Dean, St. George's Hospital Medical School; Chairman, Committee on Safety of Medicines
Professor G. Calder ✈	Chief Pharmacist, Scottish Home and Health Department
Mr M.J. Cantrell ✈	Office of the Solicitor, Department of Social Security, Department of Health
Dr J.F. Cavalla ✈	Vice-President, Research, Wyeth Research (UK) Ltd.
Mr C.J. Collins ✈	Department Director Regulatory Affairs, Europe and Export Markets, Rorer (now Rhône-Poulenc Rorer)
Mr R. Daniel ✈	Solicitor, Roche Products Limited
Professor J.A. Goldsmith ✈	Site Director Technical Operations, Roche Products Limited; Member, British Pharmacopoeia Commission; Member, ABPI Technical Committee, Europe; Visiting Professor, University of Strathclyde
Dr A.J. Grace ✈	Regulatory Affairs Manager, Rhône-Poulenc Limited (now Rhône-Poulenc Rorer)
Ms. A. Hopkins ☎	National Consumer Council
Dr R.L. Horder ✈	Director, International Development Centre, Abbott Laboratories
Mr A.W. Hunter ✈	Regulatory Controller, Wellcome Foundation Limited
Professor T.M. Jones ✈	Director Research, Development and Medical, Wellcome Foundation Limited; Member, Medicines Commission

Table 3 contd.

Professor D.H. Lawson ✈	Consultant Physician, Royal Infirmary, Glasgow; Member, Committee on Safety of Medicines; former Chairman, Committee on Review of Medicines; Visiting Professor, University of Strathclyde
Mr D. Massam ✈	Secretary, Association of the British Pharmaceutical Industry
Mrs J. McCabe ✈	Head, Drug Information Unit, Royal Infirmary, Glasgow
Mr C. Medawar ✉	Social Audit
Mr K. Miles ✉	Assistant Director, Action for Victims of Medical Accidents
Dr L. Murphy ✈	Research Scientist, Ciba-Geigy Pharmaceuticals
Mrs M.J. Nicholson ✈	Registration Adviser, E.R. Squibb and Sons Limited
Dr G.E. Overend ✈	European Regulatory Affairs Manager, Rorer (now Rhône-Poulenc Rorer)
Ms B.W. Richard ✉ ☎	Research Administrator, Center for the Study of Drug Development, Tufts University
Dr A.W. Sim ✈	Director, Organon Laboratories Ltd.
Mr R.R. Vercoe ✈	Head of Regulatory Affairs, Ciba-Geigy Pharmaceuticals
Professor S.R. Walker ✈	Director, Centre for Medicines Research
Mr N. Whiting ✈	Regulatory Affairs Manager, Roche Products Limited
Mr R.M. Whittaker ✈	Senior Counsel, Research and Development, SmithKline Beecham
Mr A.A. Willis ✈	Manager, European Affairs, Association of the British Pharmaceutical Industry
Dr S.M. Wood ✉	Head - Pharmacovigilance, Medicines Control Agency

Many past, present and future issues regarding the legislative framework were discussed at the meetings and in the correspondence. These discussions proved to be a very useful starting point for the Author's research and the following issues discussed are considered further in this thesis:

- **the deaths of human volunteers in clinical trials;**
- **the safety of herbal medicines;**

- the problems associated with unlicensed medicinal products;
- parallel imports and their potential for counterfeiting;
- the lack of information given to patients;
- hospitalisation due to adverse drug reactions;
- the risks and benefits of medicinal products;
- prescribing practices;
- the drawbacks of current postmarketing surveillance;
- the clinical trials exemption scheme;
- the high costs of licensing;
- unnecessary clinical trials;
- the development risks defence; and
- European legislation.

Safety issues relating to various medicinal products were also discussed and are considered further in this thesis: oral contraceptives; benoxaprofen (Opren); mianserin (Bolvidon, Norval); benzodiazepines; practolol (Eraldin); isotretinoin (Roaccutane); Dalkon Shield; indomethacin (Osmosin); iophendylate (Myodil); clioquinol (Entero-Vioform); phenylbutazone (Butazolidin); and oxyphenbutazone (Tandacote, Tanderil).

The discussions with the Experts listed in Table 3 verified the research emphasis of the Author's thesis, which had been outlined in the Author's draft proposals sent to these experts, and confirmed the focus which the thesis would take.

2.1.3 Formal Research Strategy

As a means of gathering information, the Author used sources such as: articles in the lay press; television programmes; cross-references from books and articles; and a general examination of the law, pharmaceutical and medical library collections in the University of Strathclyde, University of Glasgow (which is also a depository for

materials published by the European Commission) and the Drug Information Centre in the Royal Infirmary, Glasgow. These sources provided a great deal of useful background information. However, to achieve a greater depth of information, the Author constructed a "formal" research strategy, which involved a systematic check of sources. This strategy was in four stages:

1. Primary legal sources including legislation;
2. Organisations which were involved in the legislative framework;
3. Bibliographic searches; and
4. The Internet

2.2 Primary Legal Sources

2.2.1 UK Legislation and Statutory Instruments

As stated, the main aim of this thesis is to examine the effect of legislative framework on pharmaceutical innovation, consumer safety and legal redress. Therefore, the first stage in the research strategy was to obtain all the relevant UK and European legislation relating to medicinal products. Table 4 lists the primary UK legislation which was consulted.

Table 4 Primary UK Legislation Consulted (1968 - 1992)

- Medicines Act 1968
- Medicines Act 1971
- Vaccine Damage Payments Act 1979
- Consumer Protection Act 1987
- Medicinal Products: Prescription by Nurses etc. 1992

The Medicines Act 1968 sets out a basic legislative framework and, as Harrison has suggested, sets out the "general policies" to be followed.[93] Detailed provisions are contained in over 300 statutory instruments (secondary legislation). The White Paper "Forthcoming Legislation on the Safety, Quality and Description of Drugs and Medicines" set out the reasons why this style of legislation was necessary for the Medicines Act:

> " The enabling powers must be wide if the complexities of manufacture, sale and supply are to be properly covered. The Ministers' intention is not to impede the industry unnecessarily or to hamper doctors, dentists, veterinarians or pharmacists in the practice of their professions. The flexibility of the powers is intended to meet the wide variety of circumstances that can arise." [94]

However, the volume of legislation created by statutory instrument has been criticised by the Proprietary Association of Great Britain[95] and by Harrison:

> " The sheer physical bulk of this mass of material causes difficulty, not only in comprehension but also in finding the detail so often required. The situation is exacerbated by the fact that some pieces of legislation have been amended several times."[96]

Statutory instruments have also been made under powers contained in the Medicines Act 1971, Vaccine Damage Payments Act 1979 and Consumer Protection Act 1987. The provisions of various European Directives have been enacted also by statutory instrument in accordance with the European Communities Act 1972. As far as possible, every statutory instrument pertaining to medicinal products for human use was identified, obtained and examined, where relevant. Appendix III

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[93]Harrison (1986a) p.11.
[94]Cmnd 3395 (London, HMSO, 1967) p.16.
[95]Pharmaceutical Journal (1977a). This Association represents the manufacturers of non-prescription medicinal products in the UK.
[96]Harrison (1986a) p.vii.

lists these statutory instruments and the enabling legislation under which they were enacted. This appendix also states whether or not the statutory instruments have been amended or revoked. The appendix is based on information from the following combination of sources, as traditional methods used by lawyers to locate these statutory instruments proved to be inadequate. This was possibly because of the large number of statutory instruments which have been enacted then subsequently revoked or amended:

- Medicines Act Information Letters (MAILs) 1973-1996;
- United Kingdom Official Publications (UKOP) CD-ROM (which indexes HMSO publications);
- LEXIS (an on-line legal database);
- Current Law;
- Index to Government Orders (statutory instruments in force as of 31 December 1989);
- the "List of Statutory Instruments" published monthly by HMSO;
- "Guide to the Medicines Act 1968 and Associated Statutory Instruments";[97]
- "Dale & Appelbe's Pharmacy Law and Ethics";[98]
- "The Law on Medicines. Volume One. A Comprehensive Guide."[99] and
- The Internet.

It was surprisingly difficult to obtain a definitive list of statutory instruments and, despite the use of the sources above, some of the statutory instruments listed were traced only when they were mentioned in a later statutory instruments as having been revoked or amended. Throughout the writing of this thesis, the Author added to this list of statutory instruments.

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[97]ABPI (1993c).
[98]Appelbe and Wingfield (1993) and Appelbe and Wingfield (1997).
[99]Harrison (1986a).

2.2.2 European Legislation and Materials

European legislation became increasingly important in the course of researching this thesis because of the introduction on 1 January 1995 of a new licensing system in the UK, which implemented Directive 65/65/EEC. Up until this point, European legislation had seemed more like a completely separate legislative framework. The introduction of this new legislative framework integrated UK and European legislation and this will be fully discussed in Chapter 3.[100] However, this is not a European law thesis and the analysis of European law in this thesis is purely from a UK perspective.

There are various forms of European legislation and proposals:

> " In order to carry out their task and in accordance with the provisions of this Treaty, the European Parliament acting jointly with the Council, the Council and the Commission shall make regulations and issue directives, take decisions, make recommendations or deliver opinions.
>
> A regulation shall have general application. It shall be binding in its entirety and directly applicable in all member states.
>
> A directive shall be binding, as to the result achieved, upon each Member State to which it is addressed, but shall leave to the national authorities the choice of form and methods.
>
> A decision shall be binding in its entirety upon those to whom it is addressed.
>
> Recommendations and opinions shall have no binding force."[101]

European legislation relating to medicinal products is contained in a series of documents published by the Office for Official Publications of the European Communities and a list is given in Table 5. This legislation appears "as amended"

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[100] p134.
[101] Article 189 of the EC Treaty.

by subsequent legislation and has been described as a "scissors and paste version produced for the convenience of the lawyer and non-lawyer alike".[102]

Table 5 The Rules Governing Medicinal Products in the European Community (1989 - 1997)[103]

Volume I	The Rules Governing Medicinal Products for Human Use in the European Community. (1995)
Volume II	Notice to Applicants for Marketing Authorisations for Medicinal Products for Human Use in the Member States of the European Community. (1989)
Volume III	Guidelines on the Quality, Safety and Efficacy of Medicinal Products for Human Use. (1989)
Volume III	Guidelines on the Quality, Safety and Efficacy of Medicinal Products for Human Use. Addendum. (1990)
Volume III	Guidelines on the Quality, Safety and Efficacy of Medicinal Products for Human Use. Addendum No. 2. (1992)
Volume III	Guidelines on the Quality, Safety and Efficacy of Medicinal Products for Human Use. Addendum No. 3. (1996)
Volume IV	Guide to Good Manufacturing Practice for the Manufacture of Medicinal Products. (1992)
Volume V	The Rules Governing Medicinal Products for Veterinary Use in the European Community. (1993)
Volume VI	Establishment by the European Community of Maximum Residue Limits (MRLs) for Residues of Veterinary Medicinal Products in Foodstuffs of Animal Origin. (1991)
Volume VII	Guidelines for the Testing of Veterinary Medicinal Products. (1995)
Volume VIII	Establishment of Maximum Residue Levels of Veterinary Medicinal Products in Foodstuffs of Animal Origin. (1996)

However, more European legislation and proposals have been issued since these documents were published. References to these more recent items were obtained from the following sources:

- "Future Systems. A Guide to New Arrangements for the Licensing of Medicinal Products for Human Use in the European Community";[104]

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[102]Cartwright, "Introduction and History of Pharmaceutical Regulation", in Cartwright and Matthews (1991), p36.

[103] Various editions have been produced of documents in this series. A further update is planned for late 1997. These documents are published by the Office for Official Publications of the European Communities and are available from HMSO.

[104]MCA (1993l).

- EuroLaw (CD-ROM);
- Justis (official EC legal database); and
- Statutory instruments which have implemented European provisions into UK law.[105]

Appendix IV lists every European directive, regulation, decision, recommendation and opinion which relates to medicinal products or medical devices for human use, issued between 1965 and 1997. A reference to the issue of the Official Journal of the European Communities in which the legislation was originally published is given for each item. Appendix IV also includes "COM" documents relating to medicinal products. This series of documents has featured proposals for legislation, explanatory memoranda, and reports on the activities of the Committee on Proprietary Medicinal Products (CPMP).

European guidelines on the quality, safety and efficacy of medicinal products for human use, adopted by the Committee for Proprietary Medicinal Products , are also published in "The Rules Governing Medicinal Products in the European Community" series.[106] According to the Commission, these guidelines serve two purposes:

> " First, they are intended to provide a basis for a practical harmonization of the manner in which the Member States interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy contained in the Community directives. Second, they are intended to facilitate the preparation of applications for marketing authorization which be regarded as valid by all 12 Member States."[107]

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[105]For example, The Medicines (Products for Human Use - Fees) Regulations 1995. (S.I. No. 1116).
[106]Council Recommendation of 26 October 1983 concerning tests relating to the placing on the market of proprietary medicinal products, [83/571/EEC; OJ No. L332, 28.11.83, p11] and Council Recommendation of 9 February 1987 concerning tests relating to the placing on the market of proprietary medicinal products. [87/176/EEC; OJ No. L73, p1]. See also Volume III and Addenda.
[107]Commission of the European Communities (1992b), foreword.

The Commission has further stated that guidelines are used instead of directives because:

> " The use of guidelines, which are not legally binding, rather than a formal legal instrument, such as a directive, for this work, has been preferred in order to maintain an element of flexibility and not to place undue legislative restraints on scientific progress. It is recognised that in some cases, as a result of scientific developments, an alternative approach may be appropriate. However, where an applicant chooses not to apply a guideline, that decision must be explained and justified in the Expert Reports submitted by companies in support of an application."[108]

Appendix V lists all the European guidelines pertaining to medicinal products for human use which have been adopted by the CPMP, or which have been released for consultation, or which are under discussion, in the period 1983 and 1997. Many guidelines have been introduced since "The Rules Governing Medicinal Products in the European Community" were published. References to these more recent guidelines were obtained from the following sources:

- Euro Direct catalogue and order form[109];
- "Status of CPMP guidelines: guidelines published in the series "Rules Governing Medicinal Products in the European Community";[110] and
- "Guide to the European Directives concerning Medicines".[111]
- EMEA web page.

Some difficulty was experienced in compiling a fully accurate listing of these guidelines because the references in the above sources sometimes conflicted regarding the title, year, or reference number of certain guidelines.

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[108] *Ibid.*
[109] Euro Direct is the European guideline service of the Medicines Control Agency. Every issue from September/October 1993 to July/August 1996 was checked for references.
[110] Commission of the European Communities (1994).

2.3 Organisations

2.3.1 Introduction

The second stage of the research strategy was to contact organisations representing consumers, the pharmaceutical industry, professional bodies, academia and government, which had an interest in the regulation of medicinal products. The aim was to acquire a comprehensive range of specialist materials such as professional guidelines, reports, books, journals and newsletters, and keep them regularly updated. The most important sources were from the Medicines Control Agency, the European Agency for the Evaluation of Medicinal Products and the Committee on Safety of Medicines, followed by the Medical Devices Agency, the Royal Pharmaceutical Society of Great Britain, the Association of the British Pharmaceutical Industry and Social Audit. A brief outline of the functions of these organisations and the materials received and consulted, is set out in sections 2.3.2 to 2.3.8. Information and publications were also received from the Centre for Medicines Research, the Center for the Study of Drug Development, the British Institute of Regulatory Affairs, the Drug Safety Research Unit, the Proprietary Association of Great Britain, the National Consumer Council, Action for Victims of Medical Accidents, the General Medical Council, the Office of Health Economics, the Medical Benefit/Risk Foundation, the Institute of Economic Affairs, the Legal Aid Board and the Law Society of Scotland.

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[111]Charlesworth in Griffin (1992) pp33-81.

2.3.2 Medicines Control Agency (MCA)

In April 1989, the Medicines Control Agency was established. The aim of the MCA is:

> " To safeguard public health by controlling medicines thereby assisting Ministers (the "Licensing Authority") in the discharge of their responsibilities under relevant European Community (EC) Directives, the Medicines Act 1968 and the Biological Standards Act 1975 in respect of the sale or supply of human medicines in the UK." [112]

More information is given about the work of the MCA in Chapters Three and Four.[113] The following documents issued by the MCA were consulted.

A. MEDICINES ACT LEAFLETS (MALS)

These are a series of leaflets on various aspects of the Medicines Act 1968 issued by the Medicines Control Agency and, formerly, by its predecessor, the Medicines Division of the Department of Health and Social Security. Most MALs contain the disclaimer that they are

> " Only a general guide and must not be treated as a complete and authoritative statement of the law on any particular case. Copies of the Medicines Act and of the Orders and Regulations made under the Act are available from Government Bookshops."[114]

Reference was made to all of the MALs listed in Appendix VI.

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[112]MCA (1991b) p.5.
[113] p103.
[114]Medicines Division (1973a). It is easy to order statutory instruments which have been commented on in the MAL series, but, as stated earlier, the difficulty regarding statutory instruments is that there is not a definitive list available from one source which details every statutory instrument issued and its current status (eg. whether it has been amended or revoked). Therefore, without such a list finding out about statutory instruments is a complicated process.

B. MEDICINES ACT INFORMATION LETTERS (MAILS)

These constitute a series of regulatory updates featuring articles on licensing, pharmacovigilance, prosecutions, legislative changes, European requirements and developments, pharmacopoeial news, the Veterinary Medicines Directorate, and publications such as new guidance notes and leaflets. MAILs are financed by licence fees, published bi-monthly by the Medicines Control Agency and sent to all licence holders (i.e. holders of product licences, wholesale dealer's licences, manufacturer's licences, clinical trial certificates and clinical trial exemptions). They were formerly published by the Medicines Division of the Department of Health and Social Security on a less frequent basis. One Hundred and two MAILs have been issued in the period June 1973 - July/August 1997 and all were consulted by the author.

C. MLXS[115]

Section 129(6) of the Medicines Act 1968 states that, before a statutory instrument is made, Ministers must consult "such organisations as appear to them to be representative of interests likely to be substantially affected by the regulations or order". This consultation takes the form of an MLX letter. Every licence holder receives MLX letters and the "interested organisations", which receive letters are listed in Appendix VII. Every MLX relating to human medicines in the period 1990 - 1997 was examined and these are listed in Appendix VI.

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[115]It is not clear what "MLX" stands for; no clues are given on any MLX documentation.

D. MISCELLANEOUS

The MCA has issued a number of other highly useful publications which were consulted[116] and these include:

- Annual Reports of the MCA 1990/91, 1991/92, 1992/93, 1993/94, 1994/95, 1995/96 and 1996/97.
- Annual Reports of the DHSS Medicines Division 1973-1978.[117]
- Annual Symposium Posters and supplement.
- "Towards Safe Medicines."
- "Framework Document."
- "Commitment to Safety, Quality and Efficacy."
- "Future Systems. A Guide to New Arrangements for the Licensing of Medicinal Products for Human Use in the European Community".
- "Rules and Guidance for Pharmaceutical Manufacturers."

2.3.3 European Agency for the Evaluation of Medicinal Products (EMEA)

The EMEA was established in 1995 and has been described as being "at the heart of the new European system for the evaluation, authorisation and supervision of human and veterinary products".[118] The Executive Director of the EMEA stated that its four key objectives were:

" - to protect public health by mobilising the best scientific resources existing within the European Union.

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[116]Full publication details are given in the bibliography under the MCA entry.
[117]These reports are contained in the compilation of annual reports, which includes the reports of the Medicines Commission and the Committee on Safety of Medicines. The Pharmaceutical Journal (1980jj) states that the annual reports issued by Medicines Division were dropped from this compilation of reports to save money. The library at the Department of Health was unaware of the existence of the annual reports issued by Medicines Division until I contacted them. No record exists in the library as to whether or not annual reports were issued by Medicines Division in the period 1979 to 1990.
[118] EMEA (1996a) p4.

- to promote health care through the effective regulation of new pharmaceuticals and better information for users and health professionals.
- to facilitate quicker access and the free circulation of pharmaceuticals within the European single market
- to support the European pharmaceutical research and development industry by developing efficient, effective and responsive operating procedures."[119]

The EMEA consists of the Management Board, the Committee for Proprietary Medicinal Products, the Committee for Veterinary Medicinal Products and the Permanent Secretariat. The following materials issued by EMEA are consulted: [120]

- Annual Reports for 1995 and 1996;
- EMEA Directory;
- EMEA Work Programme (1997-1998);
- Press releases issued by the CPMP (1995 - 1997);
- Press releases issued by the Management Board (1994 - 1997); and
- Various consultation papers published on the EMEA's web site. [121]

More information is given about the work of the EMEA in Chapters Three and Four. [122]

2.3.4 Committee on Safety of Medicines (CSM)

The CSM was established in 1970 for the following purposes:

" a giving advice with respect to safety, quality and efficacy in relation to human use of any substance or article (not being an instrument, apparatus or appliance) to which any provision of the Medicines Act 1968 is applicable.

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[119] Ibid p6
[120] Full publication details are given in the bibliography under the EMEA entry.
[121] This web site will be discussed later in this chapter in section 2.6.

> b. promoting the collection and investigation of information relating to adverse reactions for the purpose of enabling such advice to be given."[123]

More details about the work of the CSM are given in Chapters Three and Four.[124] The CSM has issued a number of important publications, which are discussed throughout this thesis.

A. DEAR DOCTOR/DENTIST/PHARMACIST LETTERS

> " In cases of major drug safety hazards requiring immediate communication the CSM writes directly to doctors, dentists and pharmacists."[125]

Originally these letters were sent directly to doctors and dentists, but not to pharmacists. This led to complaints from pharmacists[126] and an eventual change in policy. Appendix VIII lists all the letters sent by the CSM and earlier letters sent by its predecessor, the Committee on Safety of Drugs, between 1964 and 1970.[127] It would appear from this appendix that the use of these letters has declined in recent years. This may indicate that there has not been as many "major drug safety hazards", but it is suggested by the Author that the CSM is utilising the "Current Problems in Pharmacovigilance" series of leaflets (discussed in the next page) as a means of alerting health professionals to possible hazards at a far earlier stage.

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[122]For example, p146.
[123]SI 1970/1257.
[124]For example, p114.
[125]Bem et al. (1990) p165.
[126]Pharmaceutical Journal (1973a).
[127]Bem et al (1990) also have a table but have not included the letters on methyldopa, monoamine oxidase inhibitors, benoxaprofen and aspirin.

B. ADVERSE REACTION SERIES LEAFLETS ("YELLOW PERILS")

> " Some of these have informed doctors or dentists of a newly recognised or serious hazard while others have been reminders about well-known dangers which were still causing concern, or have drawn attention to the importance of reporting suspected drug reactions." [128]

These leaflets were published by the Committee on Safety of Drugs and the Committee on Safety of Medicines. All the leaflets were consulted and are listed in Appendix VIII. [129]

C. CURRENT PROBLEMS IN PHARMACOVIGILANCE

> " This series of leaflets is intended to draw attention to problems being considered by the Committee on Safety of Medicines which are not urgent enough to need the issue of a warning in the yellow 'Adverse Reaction Series'. The subjects included may be such that a definitive statement is not possible on the basis of the data available at the time of publication." [130]

The first issue of Current Problems appeared in 1975. In the late 1970s and 1980s, only three "Adverse Reaction Series" leaflets were published and "Current Problems" appeared to assume a more important role:

> " The Current Problems series is intended to draw attention to matters of particular concern or interest which have been considered by the CSM. It also indicates some of the topics about which reports will be especially valuable. It is hoped that Current Problems will facilitate the flow of information to and from the Committee. The CSM always welcomes reports where adverse effects are

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[128]CSM (1975d).
[129]Bem et al. (1990) mention a leaflet published in December 1975 concerning megestrol acetate. However, the MCA do not have a copy of this leaflet available.
[130]CSM (1976b).

> suspected, particularly when they are clinically serious, unexpected, or when new medicinal products are involved."[131]

Current Problems is sent to all doctors, dentists and pharmacists, although it was originally sent only to hospital, and not general practice, pharmacists.[132] The most recent issues were published jointly by the Committee on Safety of Medicines and the Medicines Control Agency, and the series is now called "Current Problems in Pharmacovigilance". All the leaflets were consulted and are listed in Appendix VIII.

As was discussed earlier, the use of these leaflets has grown in importance with regard to alerting health professionals to actual and potential problems with medicinal products.

D. CSM UPDATES

> " A regular monthly column written by members and staff of the Committee on Safety of Medicines to explain and discuss the committee's role in licensing drugs and monitoring adverse effects."[133]

This column was published in the British Medical Journal throughout 1985 and 1986 but, subsequently, only one more update appeared in 1988. All the updates which were published, are listed in Appendix VIII. This series was most informative and should be restarted, in order to give more information about the work of the CSM than is contained in other publications issued by the CSM.[134]

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[131]CSM (1981a).
[132]Pharmaceutical Journal (1975a) and (1975b).
[133]CSM (1985d).
[134]The USA Food and Drug Administration publishes a monthly column in the Journal of the American Medical Association.

E. ANNUAL REPORTS

The following annual reports were consulted: Committee on Safety of Drugs (1964-1970); Committee on Safety of Medicines (1971-1996); Medicines Commission (1970-1996); British Pharmacopoeia Commission (1970-1996); Committee on Review of Medicines (1975-1992); Committee on Dental and Surgical Materials (1976-1993); and Committee on Radiation from Radioactive Medicinal Products (1979-1983).

2.3.5 Medical Devices Agency

The most important function of the Medical Devices Agency (formerly called the Medical Devices Directorate) is to ensure that:

> " All medical devices used in the UK meet the essential requirements laid down in the Directives and in so doing, do not compromise the health and safety of patients, users and, where appropriate, any other persons."[135]

The Agency issues bulletins regularly giving information on the current status of European Directives relating to medical devices. These bulletins are listed in Appendix XIX; all were consulted.

2.3.6 Royal Pharmaceutical Society of Great Britain

The Society was founded in 1841 and incorporated by Royal Charter in 1843. A Supplemental Charter granted in 1953 lays down the main objects of the Society which are:

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[135]Medical Devices Directorate (1993g).

" (1) to advance chemistry and pharmacy; (2) to promote pharmaceutical education and the application of pharmaceutical knowledge; (3) to maintain the honour and safeguard and promote the interests of the members in the exercise of the profession of pharmacy; (4) to provide relief for distressed persons, being: (i) members; (ii) persons who at any time have been members or have been registered as pharmaceutical chemists or as chemists and druggists; (iii) widows, orphans, or other dependants of deceased persons who were at any time members or registered aforesaid; (iv) students." [136]

The Royal Pharmaceutical Society issues the following publications:

A. MEDICINES ETHICS AND PRACTICE. A GUIDE FOR PHARMACISTS.

The guide describes itself as the "day-to-day reference source for practising pharmacists for a wide range of topics".[137] These topics include: a summary of the laws covering the sale and supply of human medicines, controlled drugs, veterinary drugs and non-medicinal poisons; a list of medicines for human use complete with legal classification (general sale list, pharmacy or prescription only medicine) and any additional labelling required by law; the Code of Ethics; and supplementary statements to the Code issued by the Council of the Royal Pharmaceutical Society, including guidelines on the misuse of over-the-counter medicines and dealing with clinical trials. The Guide is published twice a year and the most recent edition published in July 1997 includes new sections relating to medical devices and the promotion of medicinal products.

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[136]Appelbe and Wingfield (1997) p220.
[137]Royal Pharmaceutical Society of GB (1994).

B. BRITISH NATIONAL FORMULARY (BNF)

> " The main text consists of classified notes on drugs and preparations. These notes are divided into 15 chapters, each of which is related to a particular system of the human body or to an aspect of medical care. Each chapter is then divided into sections which begin with appropriate notes for prescribers. These notes are intended to provide information to doctors, pharmacists, nurses and other health professionals to facilitate the selection of suitable treatment. The notes are followed by details of relevant drugs and preparations."[138]

The BNF is published jointly by the British Medical Association and the Royal Pharmaceutical Society. It contains information on adverse reactions, prescribing for children and the elderly, drug interactions, liver disease, renal impairment, pregnancy, and cautionary and advisory labelling. The most recent edition of the BNF is number 34 (September 1997).

C. PHARMACEUTICAL JOURNAL

This is the official journal of the Royal Pharmaceutical Society. It is published weekly and contains articles on current affairs, adverse drug reactions, clinical pharmacy, continuing education, as well as original papers. All issues from September 1971 until 18 October 1997 were consulted.

2.3.7 Association of the British Pharmaceutical Industry (ABPI)

The ABPI is a trade association which represents over one hundred companies in Britain which manufacture prescription medicines. These companies produce over

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[138]British Medical Association and Royal Pharmaceutical Society of GB (1997).

95 per cent of the medicines which are supplied to the National Health Service.[139] Its main functions are to:

> " Maintain and improve the reputation of the industry and its contribution to the health and economic welfare of the nation; assist contact between member companies and with government departments, professional, scientific and trade organisations and other similar bodies; act as a channel of communication and to act on collective decisions taken by its members."[140]

The ABPI issues the following publications; all were consulted.

A. ABPI DATA SHEET COMPENDIUM (1995-96)

Section 96 of the Medicines Act 1968 requires product licence holders, when making a promotional representation or advertisement, to provide doctors, dentists and veterinary practitioners with a data sheet. The Medicines (Data Sheet) Regulations 1972 sets out the detailed requirements for data sheets: presentation (appearance and ingredients); uses; dosage and administration; contra-indications, warnings etc.; pharmaceutical precautions; legal category; package quantities; and any further information.[141] The ABPI compendium contains over 1800 data sheets from 134 companies. However, the list of medicinal products featured in the Compendium is not exhaustive because only information provided by member companies of the ABPI is published. Future editions of the Compendium will publish the Summary of Product Characteristics of medicinal products which are now required in place of data sheets. This is in accordance with the 1994 Regulations which are discussed in Chapter Three.[142]

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[139]ABPI (1993b).
[140]Ibid.
[141]1972/2076, as amended.
[142] p134.

B. MISCELLANEOUS

The ABPI publishes a number of other important documents which were consulted, including: "Patient Leaflet Compendium 1995-96"; "The Code of Practice for the Pharmaceutical Industry"; the "Code of Practice Review", which gives details of breaches of the Code of Practice; "Pharma Facts and Figures", which lists statistical data concerning the main activities of the UK pharmaceutical industry; annual reviews; agendas for health; and guidelines relating to the provision of computer systems to doctors, disclosure of inactive ingredients, patient information, medical experiments in non-patient human volunteers, relationships between the medical profession and the pharmaceutical industry, the manufacture of generic medicines and good clinical research practice.[143]

2.3.8 Social Audit

> " Social Audit's job is to ask timely questions about the organisations whose decisions and actions shape our lives. What, in social terms, do these organisations give to and take from the community, and how do they explain and justify what they do? Social Audit publishes reports which explain why these questions seem worth asking, and what the answers to them might be. Social Audit's concern applies to all organisations and to any government, whatever its politics. The issues may be different, but the conclusions tend to be the same: there is not enough accountability in the major centres of power. There is too much secrecy in government and in the other organisations that direct and manage our lives.[144]

Social Audit has published a number of relevant books and pamphlets, such as "Drug Disinformation", "Observations on the UK Government's 1987 Study of the Control

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[143]See the "Association of the British Pharmaceutical Industry" entry in the bibliography for publication details.
[144]Medawar (1992a) p272. The main person behind Social Audit would appear to be Charles Medawar.

of Medicines", "Power and Dependence", "Drug Diplomacy" and "Pharmaceuticals and Health Policy".[145]

2.4 Searches

2.4.1 Introduction

As was stated earlier in this Chapter,[146] it was necessary for the Author to analyse the interface of medicine, science and the law in order to fully research this thesis. As a further means of achieving this, medical, scientific and legal bibliographic indexes were consulted, to gather references to relevant journal articles and other material. This turned out to be a complicated task: the searching procedure was different for each index, the indexing terminology was also different and the indexes were in various formats (some were available on CD-ROM, others were available on-line or in printed form, one index had to be searched on CD-ROM and in printed form). Generally, searches of the printed indexes were more limiting than on-line and CD-ROM searches, as it was not possible to combine subject headings and key words, and search the index in a "free" manner. A separate search strategy, with customised search terms, had to be developed for each index. However, to promote uniformity in the searches, a core of search terms was compiled and used in each search. Table 6 lists these search terms.

The indexes were searched from January 1980 to May 1995. However, not all of the indexes were available for this period: some were not updated regularly and others did not go back as far as 1980. The most helpful indexes are listed in sections 2.4.2 and 2.4.3 and search tables are set out for most of these indexes, which list the

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[145]See separate entries in the bibliography under Medawar and Blum et al.

search terms used, the "hits" achieved by each term and, in brackets, the number of references that were deemed to be potentially useful. Reference was also made to the Science Citation Index, the International Digest of Health Legislation, Current Law, EC Infodisk and various libraries in the on-line legal database, LEXIS.

Table 6 Search Terms.

Adverse Drug Reactions; Advertising; Association of the British Pharmaceutical Industry; Clinical Trials; Committee on Review of Medicines; Committee on Safety of Medicines; Consumer Protection; Consumer Protection Act 1987; Consumer Safety; Counterfeiting; Development Risks Defence; Doctors; Documentary Evidence; Drug Information; Drug Monitoring; Drug Safety; Drug Withdrawal; Drugs; Food and Drug Administration; Food, Drug and Cosmetic Law; Generic; Group Actions; Herbal Medicine; Iatrogenic Disease; Labelling; Laws; Legal Aid; Legal; Legislation; Liability; Licences; Licensing; Malpractice; Marketing; Medical; Medical Devices Directorate; Medical Devices; Medical Ethics; Medical Jurisprudence; Medical Negligence; Medicinal Product; Medicines Act 1968; Medicines Commission; Medicines Control Agency; Medicines Division; Medicines; No Fault Compensation; Orphan Drug; Packaging; Parallel Import; Patient Information; Personal Injuries; Pharmaceutical Industry; Pharmaceuticals; Pharmacist; Pharmacovigilance; Pharmacy; Postmarketing Surveillance; Prescription; Product Liability; Product Safety; Product Surveillance; Regulation; Regulatory Authority; Vaccine Damage Payments Act 1979; Vaccine Damage; Warnings

Once the results of the searches (the "hits") had been examined, the next step was to gather the most promising materials. This involved much photocopying, borrowing of journals and very significant use of inter-library loans. The individual issues of those journals which had provided the most useful articles (based on the search references) were perused personally throughout 1995 and 1996 for recent developments not covered by the search period, and are listed in Table 7. Bibliographic indexes cannot be relied upon absolutely to reveal all the relevant information from a particular journal. This is because there are often constraints on the type and length of articles indexed. For example, although short news reports are

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[146] p22.

potentially important, they are included rarely in bibliographic indexes. In addition, a medical indexer may not have given the same emphasis to all the points that a legal researcher may have found of interest, and vice-versa. Therefore, a personal search was undertaken for additional background information in the British Medical Journal, the Lancet and the Pharmaceutical Journal. A legal journal was not chosen, because it was felt that these medical/pharmaceutical journals reported medico-legal matters more extensively and to a higher standard. This search covered the period from 1 September 1971 (when the Medicines Act 1968 came into force) until 18 October 1997.

Table 7 Journals searched "personally".

1971- 1997	
British Medical Journal	Pharmaceutical Journal
Lancet	
1994 - 1997	
British Journal of Clinical Pharmacology	Law Quarterly Review
Clinical Risk	Modern Law Review
European Law Review	New Law Journal
Journal of the Law Society of Scotland	Product Liability International/Liability Risk & Insurance

2.4.2 Medical and Scientific Indexes

A. INTERNATIONAL PHARMACEUTICAL ABSTRACTS (IPA).

IPA is published by the American Society of Hospital Pharmacists It indexes more than 600 journals and offers the pharmacist "an incomparable service for keeping up

with what is being published around the globe".[147] The subjects covered include adverse drug reactions, legislation, pharmacy practice, toxicity, sociology, economics and ethics. The printed version of this index was used and searching the index headings "laws; legislation; liability; licences; regulations" yielded the best results. However, the information retrieved was of variable quality and the emphasis of much of it was highly pharmacological.

B. INDEX MEDICUS/MEDLINE

Index Medicus is the National Library of Medicine's monthly bibliography of the literature of biomedicine. It indexes over 5000 of the world's principal medical and biomedical journals.

> " In the selection of materials for indexing, the National Library of Medicine (NLM) is advised by a chartered committee of distinguished physicians, medical editors, and medical librarians. [...] The Library indexes the literature that has been judged most useful to Index Medicus users, but it is not possible to include every journal that might contain useful articles. [...] Original journal articles are indexed, as well as those letters, editorials, biographies and obituaries that have substantive contents."[148]

The printed version of Index Medicus was searched for the years 1980 to 1987; the CD-ROM version of Index Medicus called Medline, was searched from 1988 to 1995. Index Medicus literature suggests that using MeSH (medical subject headings) terms will result usually in a more effective search than searching for words in the title or abstract. Therefore, where possible, the search terms outlined in Table 6 were matched up with a MeSH equivalent used by the Index Medicus indexers (see Table 8). In the printed version of Index Medicus, positive search

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[147]Zellmer (1988).
[148]Index Medicus literature.

results were achieved solely by using MeSH terms, thus emphasising the limiting nature of printed indexes discussed earlier. This also accounts for the observation that the searches conducted between 1980 and 1987 yielded less useful information.

Table 8 Index Medicus/Medline (1980 - 1995).

Search Term	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994/95
Advertising and drug									26(7)	35(8)	38(9)	21(7)	45(12)	49(6)	28(3)
Clinical trials standards	13(0)	36(0)	37(1)	26(1)	38(0)	23(2)	33(1)	55(0)	27(2)	37(5)	57(26)	42(4)	66(5)	108(6)	82(1)
Drug industry	61(2)	73(2)	49(2)	56(8)	80(8)	82(8)	94(7)	115(11)	170(55)	115(38)	240(89)	130(27)	273(56)	355(26)	199(15)
Drug information services		40(3)	38(0)	38(0)	44(4)	31(4)	45(1)	49(4)	80(21)	87(15)	72(8)	102(13)	73(8)	74(7)	36(1)
Drug labeling	35(0)	36(2)	35(0)	29(0)	16(3)	24(2)	32(0)	17(1)	43(3)	55(9)	31(11)	35(5)	50(11)	94(3)	63(5)
Drugs adverse effects			75(5)	71(7)	71(2)	74(10)	71(10)	86(31)	220(40)	129(21)	286(67)	264(21)	289(20)	342(4)	133(1)
Herbal and(legislation or adverse effects or regulation)									26(2)	41(1)	26(2)	23(4)	41(9)	56(0)	34(2)
Iatrogenic disease	46(0)	53(0)	45(0)	47(0)	75(0)	43(0)	52(0)	75(1)	197(1)	180(1)	165(0)	105(5)	185(3)	194(4)	117(3)
Legislation drug	79(22)	82(17)	44(14)	44(16)	61(25)	56(17)	42(19)	60(19)	156(56)	112(41)	217(85)	230(67)	277(24)	331(15)	153(8)
Legislation pharmacy	10(3)	6(1)	4(2)	3(2)	5(1)	5(5)	9(1)	17(13)	18(13)	9(4)	17(9)	19(5)	17(0)	19(2)	20(1)
Licensing and drug									5(1)	6(1)	6(3)	7(2)	16(1)	18(2)	2(0)
Marketing and drug									24(3)	50(4)	58(8)	33(6)	63(4)	85(4)	47(7)
Patient information									24(0)	30(1)	29(3)	15(1)	50(0)	44(0)	50(2)
Product liability									9(4)	8(2)	6(4)	0	4(1)	2(0)	2(0)
Product surveillance(evaluation studies 1980-87)	10(0)	4(0)	5(0)	17(5)	24(7)	20(11)	27(15)	52(27)	123(58)	74(27)	204(75)	88(21)	92(6)	132(11)	53(12)
Regulatory auth*									5(2)	10(2)	18(3)	10(0)	15(5)	11(0)	11(0)
United States Food and Drug Administration[149]	64(0)	42(1)	28(2)	32(0)	31(4)	34(1)	40(5)	33(4)	29(6)	65(8)	254(47)	252(31)	341(43)	398(16)	242(13)

[149]The Index Medicus printed version was used for the 1988 and 1989 searches, hence the lower results.

C. EXCERPTA MEDICA

Excerpta Medica selects articles from approximately 4500 journals per year and its worldwide coverage of biomedical literature concentrates in particular on European sources. Excerpta Medica is divided into fifty two sections including physiology, surgery, cancer, psychiatry and forensic science, and it is possible to subscribe to each section individually. This search was conducted on the "Drugs and Pharmacology: Abstracts and Citations" section, which was available on CD-ROM. Excerpta Medica uses a combination of descriptors (medical and drug index terms) and emtags (general indexing codes e.g. human, legal aspects), which were very easy to use. From Table 9, it can be observed that there was a significant increase in the number of articles published regarding "drug legislation" during the last 15 years.

Table 9 Excerpta Medica (1980 - 1995).

Search Term	1980-81	1982-83	1984-86	1987-88	1989-90	1991-July 1992	1993 - 1995
Adverse drug reaction and (legal aspects or regulation)	94 (4)	66 (4)	222 (14)	103 (15)	128 (24)	354 (35)	15(0)
Advertising	22 (1)	6 (2)	7 (1)	13 (2)	33 (10)	22 (1)	13(0)
Clinical trials and (legal aspects or regulation)	8 (1)	12 (6)	17 (6)	17 (8)	39 (12)	49 (6)	133(2)
Committee on Safety of Medicines	2 (0)	10 (3)	13 (5)	8 (0)	6 (6)	3 (3)	4(1)
Drug industry and (legal aspects or regulation)	13 (2)	6 (1)	31 (16)	15 (11)	59 (37)	122 (34)	51(1)
Drug information and (legal aspects or regulation)	7 (1)	9 (3)	11 (1)	12 (10)	18 (4)	86 (8)	11(1)
Drug legislation	12 (2)	8 (3)	4 (3)	21 (20)	94 (47)	163 (37)	561(26)
Drug marketing and (legal aspects or regulation)	14 (2)	7 (0)	8 (1)	10 (6)	45 (32)	96 (18)	28(1)
Drug regulation	1 (1)	1 (1)	10 (5)	6 (5)	15 (9)	5 (0)	21(3)
Drug safety and (legal aspects or regulation)	9 (1)	18 (3)	29 (6)	36 (19)	30 (20)	97 (21)	95(1)
Food and Drug Administration and (legal aspects or regulation)	22 (2)	27 (6)	29 (4)	42 (21)	100 (50)	367 (34)	81(0)
Herbal medicine and (legal aspects or regulation or adverse reactions)	3 (0)	5 (2)	12 (0)	7 (1)	21 (3)	4 (3)	7(0)
Medicines Control Agency					10 (8)	9 (6)	8(2)

Table 9 contd.

Search Term	1980-81	1982-83	1984-86	1987-88	1989-90	1991-July 1992	1993 - 1995
Prescription and (legal aspects or regulation)	33 (1)	16 (0)	31 (4)	19 (3)	64 (29)	115 (18)	58(0)
Postmarketing surveillance	6 (2)	6 (2)	21 (6)	32 (13)	34 (11)	33 (12)	102(8)
Product liability	1 (1)		3 (1)	5 (4)	4 (3)	0	25(1)
Regulatory auth*		3 (1)	12 (3)	10 (4)	29 (5)	14 (2)	17(0)

2.4.3 Legal Indexes

A. LEGAL JOURNALS INDEX

> " Covers all journal titles that are published in the United Kingdom, devoted to law or frequently contain articles on legal topics and contain original material - abstracting and newsletter services are excluded. Legal Journals Index indexes all items of a legal or semi-legal nature that are of a reasonable length. Normally this means one page or more but all original English, Scottish, Commonwealth and EEC case reports are included as are all case comments. Some administrative and tribunal decisions are excluded e.g.. planning appeals, valuation cases and social security commissioners' decisions. Book reviews of a reasonable length are indexed, as are editorials, proceedings, practice directions, questions and answers and reproductions of documents." [150]

This index was available in printed version only and was first published in 1986. It provided a limited number of useful references, as is seen from Table 10.

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[150] Legal Journals Index literature.

Table 10 Legal Journals Index (1986 - 1995).

Search Terms	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995
Class action or group action or representative action	8 (2)	9 (6)	10 (9)	3 (3)	3 (3)	4 (4)	10 (6)	0	7(4)	1(0)
Consumer Protection Act 1987		32 (0)	27 (0)	16 (1)	11 (1)	9 (1)	13 (2)	0	14(3)	3(1)
Drugs	5 (0)	14 (4)	26 (15)	14 (5)	19 (6)	29 (11)	15 (5)	8(4)	6(1)	3(0)
Pharmaceutical industry or pharmacist		1 (0)	3 (3)	8 (6)	11 (3)	11 (4)	11 (0)	7(3)	15(0)	1(0)
Product liability	60 (1)	94 (4)	66 (4)	57 (4)	61 (12)	43 (6)	66 (20)	29(1)	56(25)	9(3)

B. INDEX TO LEGAL PERIODICALS

" Legal periodicals published in the United States, and Canada, Great Britain, Ireland, Australia and New Zealand are indexed in the Index to Legal Periodicals if they regularly publish legal articles of high quality and permanent reference value. Yearbooks, annual institutes, and annual reviews of the work in a given field or on a given topic are also included. Articles must be at least five ordinary pages or two folio pages, and case notes, bibliographies, biographies, and notes of legislation at least two ordinary pages or one folio page in order to qualify for inclusion."[151]

This index was available from the on-line legal database, LEXIS. It was easy to use and provided many important references. Table 11 lists the results.

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[151]Index to Legal Periodicals literature.

Table 11 Index to Legal Periodicals (1980 - 1995).

Search Terms	1980 - 1995
Development risks defence	3 (3)
Drugs and product liability	288 (117)
Food drug cosmetic law	756 (160)
Group actions	4 (2)
No fault and not automobile and not divorce	74 (7)
Pharmacist	53 (15)

C. UNITED KINGDOM OFFICIAL PUBLICATIONS (UKOP)

" The Catalogue of United Kingdom Official Publications on CD-ROM (UKOP) is the only single source of bibliographic information on the publications of official organisations in the UK. It lists official documents published either by Her Majesty's Stationery Office (HMSO) or directly by official organisations from 1980 onwards. Also included are publications of international organisations distributed by HMSO."[152]

"Official organisations" include parliament, central government departments and organisations funded or formed by government. "International organisations" include the Council of Europe, United Nations and World Health Organisation. There are approximately 180,000 items indexed on UKOP, and included are bills, acts, debates, command papers, House of Commons and House of Lords papers, statutory instruments, annual reports and accounts, press releases, statistical tables, research documents, circulars, and periodicals. The CD-ROM was awkward to use because the search could be carried out only on individual fields as opposed to a

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[152]UKOP literature.

search of the whole database. Fields searched were Corporate Author (ca), Keyword (kw) and Title (ti). The search results are listed in Table 12.

Table 12 United Kingdom Official Publications (1980 - 1995).

Search Terms	1980 - 1995
ca = Defect Medicines Report Centre	27 (27)
ca = Medical Devices Directorate	286 (286)
ca = Medicines Commission or Committee on Safety of Medicines	46 (32)
ca = Medicines Control Agency	60 (52)
ca = Medicines Division	13 (1)
kw = Medicines	567 (329)
kw = Medicines Commission or Committee on Safety of Medicines	27 (15)
kw = Medicinal product$	37 (7)
kw = Product liability	5 (0)
ti = Consumer Protection Act 1987	6 (4)
ti = Medicines Act 1968	20 (20)
ti = Vaccine Damage Payments Act 1979	4 (1)

D. ABI/INFORM

ABI is the "oldest and largest source of periodical business information available worldwide", and indexes over 800 business and trade journals. The subjects covered include health care, marketing, advertising, and law. ABI uses a controlled term vocabulary with about 6000 standardised entries and, where possible, the search ideas were adapted to utilise this vocabulary. Table 13 lists the search results.

Table 13 ABI/Inform (1986 - 1995).

Search Terms	Dec 1986 - Aug 1992	Aug 1992 - Dec 1993	Jan 1994 - Feb 1995
(Food and Drug Administration) and pharmaceutical	268 (23)	21(0)	60(0)
Legislation and pharmaceutical	113 (8)	58(3)	44(1)
Litigation and pharmaceutical	93 (30)	42(1)	19(0)
Product liability and pharmaceutical	44 (23)	17(2)	13(0)
Product safety and pharmaceutical	36 (9)	6(0)	8(0)

E. JUSTIS

Justis is the official legal database of the European Communities and contains data from the 1960s until 1995, supplied by the European Commission. It is divided into six databases: Primary Legislation (Treaties and Agreements); Secondary Legislation (Directives and Regulations); Proposed Legislation; National Implementation; Reports of the European Court of Justice; and Parliamentary Questions. The "Secondary Legislation" and "Proposed Legislation" databases were searched and the search term "medicinal products & !veterinary"[153] yielded useful results:

- *Secondary Legislation - 82 hits (42 relevant references)*
- *Proposed Legislation - 86 hits (29 relevant references)*

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[153]"& !" = "and not".

2.5 The Internet

In the last stage of this research, the Author has gone "on-line"[154] and has used the Internet as a means of keeping up-to-date with recent developments relating to the regulation of medicinal products. As will be appreciated, the material covered in this thesis is constantly evolving and the Author found that the Internet was an effective means of contacting many of the organisations mentioned in previous sections, gathering new statutory material, and reading recent issues of journals such as The Lancet and the British Medical Journal. It was not felt necessary to repeat the CD-ROM searches outlined in section 2.4, as the most useful of the bibliographic indexes, Medline was available on the Internet, and the Author was able to check articles which were of interest and had been recently published.

Table 14 lists various web-sites which were found to be of use, complete with their web address and contents of their web page.[155]

Table 14 Internet Websites consulted

Organisation *Web Address*	• Contents of web page.
Association of the British Pharmaceutical Industry (ABPI) *[http://www.abpi.org.uk/]*	• sets out the objectives of the ABPI • lists member companies of the ABPI and gives links to their home pages • links to the Office of Health Economics and the Centre for Medicines Research International • links to regulatory agencies, health and government agencies, the European Union, pharmaceutical organisations/societies, trade associations, general regulatory and pharmaceutical information, other sites of general interest and specialist areas of medicine

[154] fitzgerald@easynet.co.uk.
[155] Information on the use of the Internet for legal and medical research can be found in Pallen (1997), McGregor (1997) and Kiley (1996).

Table 14 contd.

British Institute of Regulatory Affairs (BIRA) *[http://www.bira.org.uk/]*	• general introduction to regulatory affairs • guide to legislation - this is to be developed • links to newsgroups
British Medical Journal *[http://www.bmj.com/]*	• Indexes of current and past issues (1995 - 1997) • full text of selected items • links to the BMA
CNN Health News *[http://www.cnn.com/HEALTH/]*	• lists health news articles from around the world
Committee on Safety of Medicines (CSM) *[http://www.open.gov.uk/mca/csmhome.htm/]*	• sets out the activities of the CSM • explains its working arrangements • lists membership of the CSM, its Sub-Committees and Expert Advisory Panel • gives CSM contacts • explains the yellow card scheme and lists recently introduced medicinal products with "black triangle" status • full text of current problems in pharmacovigilance (1996-1997) • full text of most recent Dear Doctor letter regarding terfenadine
Europa **(The European Union's server)** *[http://europa.eu.int/]*	• gives access to official press releases of the European institutions and information on future events, statistics, publications and databases • explains the role of the various European Institutions • gives information on the European Union's activities in economic and social matters, security and foreign policy, justice and home affairs • has search options and it was possible to execute a search using the term "medicinal product" to pinpoint recent European developments which were of relevance to this thesis

Table 14 contd.

European Agency for the Evaluation of Medicinal Products (EMEA) *[http:/www.eudra.org/]*	• full text of EMEA's Work Programme 1997-98, EMEA Directory, documents for consultation, and CPMP/CVMP calendar 1996/97 • full text of EMEA Management Board press releases and reports (1994-1997) • CPMP press releases, and standard operational procedures (index only) (1995-1997) • full text of selected European guidelines • European Public Assessment Reports • pharmacovigilance documentation • EMEA human unit newsletters • CVMP press releases
HMSO *[http://www.hmso.gov.uk/]*	• publishes the full text of Acts of Parliament and Statutory Instruments implemented in 1997
Journal of the American Medical Association *[http://www.ama-assn.org/]*	• index of past issues • selected articles available in full text
Lancet *[http://www.thelancet.com/]*	• Index of current and back issues • full text of selected articles • search facility
Medical Devices Agency (MDA) *[http://www.medical-devices.gov.uk/]*	• sets out the aims of the MDA and its roles and responsibilities • explains how the MDA works • lists contacts within the MDA • defines medical devices • index of European Directives and Statutory Instruments relating to medical devices • full text of Directives Bulletins • full text of Guidance on the EC Medical Devices Directives • Index of MDA Circulars, (Safety Notices, Hazard Notices, Pacemaker Technical Notes) • full text of the MDA's Annual Report and Business Plan • Device Evaluation publications (catalogue), • Reports (e.g. "Transfer of neonates in ambulances" and "Global harmonisation task force" • guidance on reporting adverse incidents involving medical devices

Table 14 contd.

Medicines Control Agency (MCA) *[http://www.open.gov.uk/mca/]*	• information on the activities of each division of the MCA • information on the withdrawal of fenfluramine and dexfenfluramine • information on HRT and breast cancer • links to CSM page
National Library of Medicine *[http://www4.ncbi.nlm.nih.gov/PubMed/]*	• Medline search facilities
New England Journal of Medicine *[http://www.nejm.org/]*	• Selected articles available in full text in current and past issues • facility to search past issues
Pharmaceutical Information Network - PharmInfonet *[http://www.pharminfo.com]*	• search engine to look for articles of pharmaceutical relevance • contains articles, drug information, publications, discussion groups and information on particular diseases
PharmWeb *[http://www.pharmweb.net/]*	• Provides links to a great deal pharmacy information • PharmWeb world drug alert (under development - to be used for sending emergency drug alerts) • PharmWeb discussion forum (discussion groups and mailing lists) • patient information • PharmWeb directory - directory of health professionals • lists publications, conferences and meetings • PharmWeb yellow pages -lists companies, pharmacists and hospitals on the Internet • links to government and regulatory bodies around the world
UK Department of Health *[http://www.open.gov.uk/doh/]*	• information to the public/media regarding current issues (e.g. CJD, health advice for travellers) • information about the DoH (responsibilities, Ministers, research and development, complaints procedures, economics, statistics & analysis and information on agencies • press releases (full text 1995-1997) • full text of publications (departmental circulars, white and green papers, • index of statistical publications DoH booklets and leaflets

Table 14 contd.

United Kingdom Parliament *[http://www.parliament.uk]*	• information on the activities of the House of Commons • information of the activities of the House of Lords • Parliamentary bookshop - index of publications • Parliamentary archives - index • full text of Hansard • Select Committees reports • full text of Government press releases
US Food and Drug Administration *[http://www.fda.gov/]*	• FDA news relating to foods, human drugs, biologics, medical devices/radiological health, animal drugs, cosmetics, field operations/imports, toxicology, international, medical products reporting, children and tobacco • information relating to cancer, breast implants, and BSE • text of the food drug cosmetic act is available • guidance documents • good manufacturing practice notes
World Health Organisation *[http://www.who.ch/]*	• general information on WHO • publications can be downloaded

The Author found that the website operated by the EMEA was the most useful, following by the MDA's website. The EMEA does not have an equivalent of the MCA's Information Centre, which the Author has found to be most efficient in dealing with telephone enquiries. Instead, the EMEA seems to have concentrated its efforts on making its publications available from its website. The Author would like the CSM and MCA to follow the lead of the EMEA and have more information available on the Internet.

The Author understands that the MCA proposes to review its website in the near future. It is suggested by the Author that press releases should be issued on this website following meetings of the CSM, in the same way as is done by the CPMP

and the Management Board of the EMEA. It would also be useful if the MCA published MLXs on its website and gave regular updates on its activities. Perhaps for the future, it would also be useful if the MCA could publish information relating to medicinal products, which could be accessed by patients.

2.6 Conclusions

In the course of researching this thesis, the Author has concentrated on examining published sources rather than conducting empirical research. The interviews which were conducted with the experts listed in Table 3 were done on an "off the record" basis because the interviewees felt more comfortable with this, possibly because of the commercial sensitivity of the issues discussed in this thesis. It was felt that further interviews would have also been done on the same basis and sources would not have wished to have been quoted.

Although comparative materials were gathered from jurisdictions such as USA, Japan, Australia and Canada, it was decided to focus on the legislative framework in the UK because there was plenty of new material to analyse. The Author did not contact the European Commission for comment as there were plenty of primary European sources to analyse.

As the research strategy for this thesis evolved, the Author concluded that the most useful tool for examining primary as well as secondary materials at the interface of medicine, science and the law was the Internet. Although use of the Internet does not completely replace the need to use more traditional bibliographic search indexes in the initial stages of research, it does replace the need to keep visiting the library for the purposes of keeping up-to-date with new developments and the need to contact organisations in order to obtain copies of new material, as most organisations make new material available on the Internet. New information

and websites relevant to medicinal products appear on a regular basis. Some websites such as the Houses of Parliament site are updated on a daily basis. Also, the most useful bibliographical index, Medline, can be searched for free on the Internet.

A copy of the Food, Drug and Cosmetic Act is available on the FDA's website and it is suggested by the Author that access to an overview of the legislative framework operating in the UK on the MCA's website would be extremely helpful. Unfortunately, the legislative provisions relating to medicinal products are scattered throughout UK and European legislation, which has been constantly amended (and not to any great extent consolidated), and it may be too ambitious to hope that this information could be available on the Internet. Transparency relating to the activities of the regulatory agencies is to be encouraged and this could be achieved by development of the information available on the Internet.

In the course of utilising all the research techniques outlined throughout this Chapter, a great deal of material was obtained which was ultimately deemed to be surplus to the consideration of the legislative framework. This material covered issues which included: clinical trials (it was judged that pharmacovigilance was a more important matter to be examined); the development of treatments for AIDS; generic medicinal products (there was a health scare with generics in USA but no problems were experienced in the UK or Europe); the pricing structure relating to medicinal products; and, patent and trademarks. These issues are listed in Chapter 5 as being areas for possible future research.[156]

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[156] p326.

Chapter Three

The Development of the Legislative Framework following Thalidomide

Part I

Introduction

3.1 Structure of this Chapter

As discussed in Chapter One, thalidomide is widely regarded as being responsible for law reform in the UK, Europe and many other countries.[157] In the UK, a legislative framework relating to medicinal products was introduced following thalidomide. It is argued in this thesis that this framework encompasses a product liability scheme (which applies to all types of products) and a regulatory scheme specifically relating to the control of medicinal products.

In this Chapter, in relation to the product liability scheme, the Author will discuss the various proposals for legislative reform which impacted on the UK. These comprised proposals from the English and Scottish Law Commissions, the European Commission and the Pearson Commission. The Author will also discuss the major resulting legislation from the European Directive on Liability for Defective Products which followed the implementation of this Directive into UK law, namely the Consumer Protection Act 1987. This discussion will be presented chronologically

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[157] p6.

(as this was the most logical and least confusing approach) and will examine the historical background as well as the current legislative framework.

The Author found that the discussion of the regulatory scheme controlling medicinal products is more complicated in that on 1 January 1995, a new regulatory scheme was introduced by The Medicines for Human Use (Marketing Authorization Etc.) Regulations 1994 (the "1994 Regulations"). The 1994 Regulations implemented the provisions of various European Directives and the objective was to harmonise UK provisions with the provisions in other Member States. These Regulations replaced an earlier scheme under the Medicines Act 1968 and consequently replaced the Act as the legal basis for licensing the majority of medicinal products. However, as will be discussed later, many provisions of the Medicines Act 1968 are still in force and, unfortunately, there has been no consolidation of the legislation. In the opinion of the Author, this has led to there now being an unwieldy and complicated regulatory framework which encompasses UK and European legislation, and also self-regulatory codes such as the Code of Practice for the Pharmaceutical Industry (this Code will be discussed in Chapter Four).[158]

In this Chapter, the Author has presented the discussion of this regulatory scheme as follows:

1. The Development of Regulation in the UK

This will include a discussion of: early legislative controls and the influence of thalidomide, proposals for reform; the work of the Committee on Safety of Drugs; the introduction and structure of the Medicines Act 1968 (mention will be made of its key provisions); and the administration of the licensing by various regulatory

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[158] p250.

bodies (including the Medicines Control Agency, Medicines Commission, Committee on Safety of Medicines and British Pharmacopoeia Commission which still operate under the 1994 Regulations).

2. *The New Licensing System*

This will include a discussion of: the proposals for European harmonisation; the introduction of the 1994 Regulations and the effect on the Medicines Act 1968; key provisions of the 1994 Regulations; and the administration of these Regulations including reference to the European Agency for the Evaluation of Medicinal Products and the Committee on Proprietary Medicinal Products.

Part II

The Development of a Product Liability Scheme

3.2 Proposals for Reform

" This capricious nature of the law on liability for defective products was illustrated by the Thalidomide tragedy, the victims of which had to rely on extra-legal payments of compensation. It was this disaster which proved to be the catalyst for the whole debate on product liability throughout Europe, causing a number of major inquiries into the subject to be mounted in the 1970s." [159]

In relation to product liability, Lord Griffiths, speaking in 1989,[160] commented that the law had "hardly advanced a step" since the case of *Donoghue v Stevenson* in 1932.[161] However, on 2 November 1971, the Law Commission and the Scottish Law Commission had been asked:

" to consider whether the existing law governing compensation for personal injury, damage to property or any other loss caused by defective products is adequate, and to recommend what improvements, if any, in the law are needed to ensure

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[159]Clark (1987) p11.
[160] Transcribed from a tape of a speech made by Lord Griffiths in 1989.
[161][1932] A.C. 562. See Clark (1987) and Pearson (1978a) for a discussion of the legislative position in the UK prior to reform by the Consumer Protection Act 1987.

> that additional remedies are provided and against whom such remedies should be available." [162]

The Commissions set up a joint Working Party, produced a "joint consultative document" in 1975[163], published their final report in June 1977[164] and concluded that a system of strict liability for defective products should be introduced. During the consultation process, the Commissions had been informed of three reasons why medicinal products should be treated differently from other types of product:

> " One was the argument that drugs only combat pain or disease by interfering with the natural processes of the body and that if drugs were completely safe they would not work; it was urged that a general standard of safety was inappropriate to drugs. The second point was that many drugs are only available on prescription and the suitability of the particular drug for the particular patient is monitored by persons and bodies other than the producer of the drug, including the medical practitioner who makes out the prescription. The third argument was that the imposition of strict liability on producers of pharmaceuticals might inhibit research into new products and retard the availability to the public of new medicinal remedies." [165]

The Scottish Law Commission felt that there might be grounds for special legislative provisions for medicinal products. However, the conclusions of the Law Commission were more categorical:

> " All the policy considerations in favour of imposing strict liability on producers apply with as much force to pharmaceuticals as they do to other products. The producer of defective pharmaceuticals creates the risk; he is the person best able to control the quality of the product; he is the person best able to insure against claims; and public expectation that drugs on the market will be safe is raised by

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[162]Law Commission and Scottish Law Commission (1975) p1.
[163]Ibid.
[164]Law Commission and Scottish Law Commission (1977).
[165] Ibid p19.

> advertising and by the promotional material with which the pharmaceutical industry supply the medical profession. Finally the thalidomide case itself, the history of which is too well known to need recounting, illustrates the procedural and evidentiary problems that face the claimant who seeks compensation under the existing law." [166]

On 19 December 1972, the Prime Minister, Edward Heath, announced the decision to set up the Royal Commission on Civil Liability and Compensation for Personal Injury (the "Pearson Commission"):

> " The Government have been considering proposals made from time to time in the past, which are now particularly relevant in the light of the Report of the Robens Committee on Safety and Health at Work and in connection with the recent concern over the thalidomide cases, that there should be an inquiry into the basis of civil liability in the United Kingdom for causing death or personal injury. It is the Government's view that a wide-ranging inquiry is required into the basis on which compensation should be recoverable." [167]

The Pearson Commission was established on 19 March 1973 and its terms of reference were:

> " To consider to what extent, in what circumstances and by what means compensation should be payable in respect of death or personal injury (including ante-natal injury) suffered by any person -
>
> a. in the course of employment;
>
> b. through the use of a motor vehicle or other means of transport;
>
> c. through the manufacture, supply or use of goods or services;
>
> d. on premises belonging to or occupied by another;

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[166]Ibid p21.
[167]Pearson (1978a) p3.

> e. otherwise through the act or omission of another where compensation under the present law is recoverable only on proof of fault or under the rules of strict liability,
>
> having regard to the cost and other implications of the arrangements for the recovery of compensation, whether by way of compulsory insurance or otherwise." [168]

In 1978, the Pearson Commission published its report and concluded that a system of strict liability for defective products should be introduced.[169] The Pearson Commission also considered whether medicinal products should be excluded from this system of strict liability or subject to special treatment. The Medicines Commission (discussed later in this Chapter[170]) had given evidence to the Pearson Commission and had expressed the hope that:

> " any adjustment or revision in the present system of liabilities and compensation that might be adopted would not have any deleterious effect either on the standard of patient care, standards of research or the development and testing of new medicines, arising from fear of possible product liability, which might be felt by any person or organisation involved in health care or research.[171]

The Association of the British Pharmaceutical Industry (ABPI) also gave evidence and suggested that a State-assisted compensation scheme should be introduced.[172] Despite this evidence, the Pearson Commission concluded that medicinal products should not receive special treatment.[173]

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[168]Ibid. The Law Commissions and the Pearson Commission all acknowledged that there was a degree of overlap in their respective terms of reference. The Pearson Commission stated that they had "benefited from these concurrent deliberations" [Pearson (1978a) p256].

[169]For further information see Gamble and Forte (1978), British Medical Journal (1978a) and Fleming (1979).

[170] p111.

[171]Medicines Commission et al (1975) p. 10.

[172]Pharmaceutical Journal (1978l).

[173] " Drugs represent the class of product in respect of which there has been the greatest public pressure for surer compensation in cases of injury. The application of strict liability to drugs, however, is subject to a number of particular problems. We are concerned here not so much with proprietary medicines which are sold direct to the public as with medicines which are available only on prescription. It is these which carry a real, if small, risk of catastrophe. In the light of our decision not to recommend either a special defence for

The ABPI and the Medicines Commission responded strongly to the recommendations of the Pearson Commission and both issued statements.[174] The Medicines Commission commented:

> " The Medicines Commission has serious reservations about the practicality of applying the concept of product liability to medicines without there being extensive further consultation. The Medicines Commission finds it difficult to envisage that any other industry would be faced with a comparable totality of complexities, difficulties and anomalies." [175]

At the same time, proposals relating to liability for defective products were being discussed in Europe. In 1976, the European Commission published a "Proposal for a Council Directive relating to the Approximation of the Laws, Regulations and Administrative Provisions of the Member States concerning Liability for Defective Products".[176] In 1977, the Council of Europe published the "Convention on Products Liability in regard to Personal Injury and Death" (the "Strasbourg Convention").[177] Both of these European proposals were examined by the Pearson Commission and by the Scottish and English Law Commissions. The Law Commissions were very

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development risks or a financial limit on liability, the case for special treatment may be thought the stronger.
There are other, related, considerations. The injured person would still have to prove causation, and there could be particular difficulties in tracing the cause of the injury to the drug. We have been informed by the Medicines Commission that, because of the many formidable difficulties involved, "it is improbable that any practicable programme of testing could offer an absolute safeguard". The responsibility for safety rests not only on manufacturers and the Committee on Safety of Medicines, but also on the doctors who prescribe. It has been made clear to us that the pharmaceutical industry is opposed to strict liability.
We acknowledge the force of these arguments, and we recognise that the difficulties faced by drug manufacturers would if anything be aggravated by the imposition of strict liability. We have nevertheless concluded that no special treatment could be justified. The demand for fuller and surer compensation for injuries caused by drugs is now an international phenomenon. The context is one in which the industry finds itself under pressure, whatever its legal liabilities in any one country. These difficulties, and the more fundamental problem of trying to produce safe drugs would not be solved by avoiding a change to strict liability in the United Kingdom."

Pearson (1978a) pp272-273.

[174]See Pharmaceutical Journal (1978l) and Medicines Commission et al (1979) pp18-19.

[175]Medicinal Commission et al (1979) p19.

[176]This proposal and its explanatory notes are reproduced in Law Commission and Scottish Law Commission (1978).

[177]This Convention and its Explanatory Notes are also reproduced in Law Commission and Scottish Law Commission (1978).

critical of the European Commission proposal and stated that it had many "objectionable features", dealt "inadequately or wrongly with four topics" and

> " even if amended to take account of the points made above, would be detrimental to the further development and reform of the law of the United Kingdom in respect of liability for defective products." [178]

By 1978, there were four major UK and European sets of proposals relating to liability for defective products. Of these proposals, it was the European Commission's Proposal for a Council Directive which achieved "primacy";[179] according to Lord Griffiths:

> " We delayed legislating because of the probability that a Directive would finally emerge from the European Community, which it would be our duty as a member of the Common Market to implement in our own domestic law." [180]

3.3 The European Directive on Liability for Defective Products

> " In the late 1970s and early 1980s, it was commonly felt among industry that the Products Liability Directive was going nowhere. It was confidently predicted that a Conservative government in the United Kingdom could not possibly abandon hundreds of years of legal tradition that links liability to fault.
> But in July 1985, Prime Minister Margaret Thatcher's government did precisely what it was not expected to do. It permitted the adoption of the Directive and broke the link between legal liability and negligence." [181]

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[178]Ibid p49.
[179]Clark (1989a).
[180]Transcribed from a tape of a speech made by Lord Griffiths in 1989.
[181]Schneebaum (1989) p284.

The progress from Proposal to Directive was problematic: negotiations within the European Community continued over a ten year period and Stapleton described "deep divisions" within the Member States.[182]

> " Eventually, by allowing Member States to derogate from the Directive on three issues, a somewhat reluctant consensus was achieved in 1985 and a final Directive was adopted by the Council of Ministers."[183]

These issues related to agricultural products, a development risks defence and a financial ceiling on liability. Hodges has described these options to derogate as "built-in obstacles to achieving approximation of the national laws".[184] However, he acknowledged that the options were "the price for achieving unanimity".

The preamble to "Council Directive of 25 July 1985 on the approximation of laws, regulations and administrative provisions of the Member States concerning liability for defective products" sets out the reasons for its implementation:

> " Approximation of the laws of the Member States concerning the liability of the producer for damage caused by the defectiveness of his products is necessary because the existing divergences may distort competition and affect the movement of goods within the common market and entail a differing degree of protection of the consumer against damage caused by a defective product to his health or property. [...]
>
> Liability without fault on the part of the producer is the sole means of adequately solving the problem, peculiar to our age of increasing technicality, of a fair apportionment of the risks inherent in modern technological production." [185]

The contents of the Directive are set out in Appendix IX.

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[182]Stapleton (1994) pp47-49.
[183]Ibid.
[184]Hodges (1996).
[185]85/374/EEC.

In November 1995, the Department of Trade And Industry (DTI) published an explanatory and consultative document to provide information and gauge opinion on the provisions of the Directive.[186] In relation to medicinal products, the DTI document highlighted two special problems. Firstly, the definition of "producer" in Article 3[187] and, secondly, the definition of "defective" in Article 6.[188]

Following much Parliamentary Debate, the provisions of the European Directive were implemented into UK law by Part I of the Consumer Protection Act 1987.[189] This Act came into force on 1 March 1988. Part I of the Act consists of 9 sections which are listed in Table 15.[190]

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[186]Department of Trade and Industry (1985).

[187] " The position of pharmacists, doctors, nurses and others operating in the health sector requires particular consideration. Many doctors and health care personnel are the last link in the chain of supply of medicines from manufacturer to patient, and as such might be liable under the provision of this Article when the producer of a defective medicinal product could not be identified. However, for NHS staff, the supplier would be the health authority, not the member of staff concerned. It is expected that the authority's records would need to provide particulars of the sources of its drugs if it is to be sure of avoiding liability under the Directive. Some health care personnel such as general medical and dental are not employees of health authorities but are self-employed and under contract to the authorities. Their position is similar to that of retail pharmacists who would be expected to maintain adequate records or, in the absence of such records, to be subject to liability when the producer cannot be identified. It should be stressed that the exercise of clinical judgement in favour of one medicinal product rather than another will not of itself create a liability under the Directive on the part of the medical practitioner concerned for damage caused by the product; nor will the exercise of such judgement of itself affect the patient's right of action against the producer." Ibid p11.

[188] " The safety which a person is entitled to expect raises particularly complex issues in respect of medicinal products and adverse reactions to them. Establishing the existence of a defect in a medicine administered to a patient is complicated by the fact that not only is the human body a highly complex biological organism, but at the time of treatment it is already subject to an adverse pathological condition. In order to avoid an adverse reaction, a medicine will have to be able to cope successfully with already faulty organs, disease, and almost infinite variations in individual susceptibility to the effect of medicines from person to person. The more active the medicine, and the greater its beneficial potential, the more extensive its effects are likely to be, and therefore the greater the chances of an adverse effect. A medicine used to treat a life-threatening condition is likely to be much more powerful than a medicine used in the treatment of a less serious condition, and the safety that one is reasonably entitled to expect of such a medicine may therefore be correspondingly lower.
Attention would also have to be paid to related environmental factors (emergency or routine, method of administration, situation and supervision etc.) and to possible interactions and correlations between the various factors, for example between a patient's diet and the medicine, or published warnings and the patient's ability or opportunity to understand them. These are all circumstances which should be taken into account in determining the level of safety a person is reasonably entitled to expect, and hence in determining whether a particular medicinal product is defective." Ibid p13.

[189]First reading [482] (19.11.86) 233; Second Reading and Committed to a Committee of the Whole House (8.12.86) 1003-62; Committee [483] (19.1.87) 715-75, 781-808; (20.1.87) 818-48, 865-80, 881-92; (29.1.87) 1463-512, 1518-38; Report [485] (9.3.87) 824-34, 840-78, 886-922; (12.3.87) 1140-57, 1167-93; Third Reading, passed and sent to Commons (19.3.878) 1519-40; Amendments considered [487] (14.5.87) 784-98; Royal Assent (15.5.87) 821.

[190]For a discussion of the provisions of the Act see Clark (1987) and Blaikie (1987).

Table 15 Framework of Part I of the Consumer Protection Act 1987.

Section 1	Purpose and Construction of Part I
Section 2	Liability for Defective Products
Section 3	Meaning of "defect".
Section 4	Defences
Section 5	Damage giving rise to liability.
Section 6	Application of certain enactments etc.
Section 7	Prohibitions on exclusions from liability.
Section 8	Power to modify Part I.
Section 9	Application of Part I to Crown.

In relation to the options to derogate given in the Directive, the United Kingdom has decided not to include primary agricultural products, not to exclude a development risks defence and not to set a ceiling on financial liability.

In its "First Report on the application of Council Directive on the approximation of laws, regulations and administrative provisions of the Member States concerning liability for defective products" published in accordance with Article 21 of the Directive, the European Commission stated that all member States except for France, have taken measures to implement the Directive into national law.[191] Appendix X sets out the details of how each Member State has implemented the Directive and which (if any) options have been exercised.[192]

In their report, the Commission also made the following comments regarding the operation of the Directive:

> " The Directive is generally perceived to have been an important piece of legislation. It has contributed towards an increased awareness of and emphasis on product safety. The Directive has eased the burden on the Plaintiff in proving his case. At this moment, the Directive does not appear to have had the effect of

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[191]Commission of the European Communities (1995).
[192]Ibid.

> increasing the number of claims made, nor does there appear to have been an increase in the level of insurance premiums as a consequence of the Directive. However, experience is still limited and is only likely to develop slowly. For example, there is only limited jurisprudence from all the Member States and to date no national court has referred any question of interpretation to the European Court."[193]

Christopher Hodges, who works for a London firm of solicitors, McKenna & Co, had been asked by the Commission to conduct a study to "clarify the effects and experience" of the Directive.[194] Hodges sent questionnaires to governments, manufacturers, Chambers of Commerce, insurers and consumer organisations throughout the European Community. Hodges also examined cases involving the application of the Directive: in 1994, there were only three judgements and these involved a mountain bike (Italy), advent candles and wood paint (both Germany). To date, no reported cases have involved medicinal products. Based on Hodge's study, the Commission further stated in its First Report:

> " Regarding the application of the Directive, the Commission does not consider it necessary, at this stage, to submit any proposals for amendment to the Directive. Nevertheless, certain aspects of the Directive concerning the protection of consumers and the functioning of the Internal Market require continued monitoring. This is the case, for example, with the exclusion by the majority of Member States of unprocessed agricultural products, whose impact the Commission will evaluate." [195]

This is the most recent statement on the implementation and application of the European Directive on liability for defective products; the next policy review will take place in five years. Hodges commented:

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[193] Commission of the European Communities (1995) p2.
[194] Hodges (1993).
[195] Commission of the European Communities (1995) p2

> " It is a source of disappointment to manufacturing and insurance industries and consumer interests that the opportunity has not been taken to harmonise product liability law further by removing the ability of Member States to select from the three optional provisions. These divergences, particularly in relation to unprocessed food and the development risks defence, provide an endless source of confusion and unnecessary complication. Nevertheless, it is clearly in industry's interest to have a period of stability with no change to the Directive, rather than to accept a number of potentially destabilising changes, notably a total abolition of the development risks defence which had been proposed by consumer interests." [196]

3.4 Conclusions

In the early stages of researching this thesis and assessing whether the legislative framework had achieved a balance between pharmaceutical innovation, consumer safety and legal redress, the Author placed as much weight on researching the effect of the product liability scheme on this balance as researching the effect of the regulatory scheme controlling medicinal products on this balance. However, it is now the Author's opinion that the product liability scheme has not affected the legislative framework to the same extent as the Medicines Act 1968 and the 1994 Regulations. Consequently, the Author has placed more emphasis on discussing these legislative provisions rather than the provisions of the Consumer Protection Act 1987. The only aspect of the product liability scheme which potentially affects the balance of the legislative framework is the development risks defence and it is discussed in Chapter Four.[197] Additionally, this thesis considers the relative impact of both the product liability and regulatory schemes on the balance between

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[196]Hodges (1996) p21.
[197]p290.

pharmaceutical innovation, consumer safety and legal redress which has been achieved by the legislative framework.

Part III

The Development of the Regulation of Medicinal Products

3.5 The Regulatory Framework prior to 1995

3.5.1 The Influence of Thalidomide

In the United Kingdom, legislation relating to the control of medicinal products originated in the mid-nineteenth century, and focused initially on the regulation of poisons[198] and the professional conduct of pharmacists.[199] Mann suggested that "modern concepts of the control of drug safety" derive from the Therapeutic Substances Act 1925.[200] Following this Act, legislation relating to medicinal products developed sporadically, and Harrison commented:

> " By the late 1950s, many of the more objectionable activities associated with the manufacture, distribution and promotion of medicines had been stopped and with such a variety of legal controls over medicines one might see little scope for, or

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[198]For example, the Arsenic Act 1851 was deemed necessary because "the unrestricted sale of arsenic facilitates the commission of crime", Appelbe and Wingfield (1997) pXXV.

[199]For example, the Pharmacy Act 1852 sets out the framework and powers of the Pharmaceutical Society of Great Britain. Much earlier regulations have been traced back several thousand years to China, Egypt and Greece, and controls in the United Kingdom have been traced back to Ordinances of the Gild of Pepperers of Soper Lane, published in 1316. See "Pharmaceutical medicine and the law: an historical perspective", in Goldberg and Dodds-Smith (1991), Hartley (1982) and Penn (1979) for historical overview of early regulation. See Mann (1984) and Sneader (1985) for a history of the development of medicines.

[200]Mann (1988a) p725. This Act "controlled by licence the manufacture (but not the sale or supply) of a limited number of products the purity or potency of which could not be tested by chemical means. These included vaccines, sera, toxins, antitoxins and certain other substances. The list was greatly extended when antibiotics came into use", Appelbe and Wingfield (1997) p.XXVII.

> point in, further legislation on the subject. In fact, however, the protection given to the professions and to the public was more apparent than real as many people pointed out. The legislation had been made piecemeal to remedy a particular evil and consequently, there were loopholes and anomalies." [201]

Several authors have discussed missed opportunities for improvements in the legislation relating to medicinal products. Mann highlighted the "Report from the Select Committee on Patent Medicines, together with the Proceedings of the Committee, Minutes of Evidence and Appendices", which was published in 1914, but the proposals were not implemented.[202]

> " Thus, but for the outbreak of World War I, a Medicines Commission and formal drug regulatory body, concerned with appliances as well as medicines, might well have existed in Britain *before* most of the instruments of modern therapeutics were in place. If this control had been extended, as experience was gathered, to the marketing of new drugs, then some of the iatrogenic hazards of the last 25 years might well have been lessened or prevented. It is not altogether fanciful to look upon the children of the thalidomide disaster as late and unwitting victims of World War I." [203]

In the opinion of Hodges and Appelbe, "one of the many ignored warnings of inadequate drug testing" was an article written by Dr George Discombe in 1952, and published by the British Medical Journal, which discussed the problems associated with the use of amidopyrine.[204] Hodges and Appelbe also mentioned a report published by the World Health Organisation in 1957, which they suggested:

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[201]Harrison (1986a) p7. For example, the Cancer Act 1939 controlled the availability and advertising of remedies for cancer. See Hodges and Appelbe (1987a), (1987b) and Appelbe and Wingfield (1997) for more information on the history of the development of legislation.
[202]Published by HMSO.
[203]Mann, R.D., "The Historical Development of Medicines Regulations.", in Walker and Griffin (1989), pp.3-15, at p13.
[204]Hodges and Appelbe (1987a) p121.

> " outlined procedures which, had they been followed, would have avoided much of the tragic consequence of the marketing of thalidomide.".[205]

Another author, Harrison, mentioned an inter-departmental working party set up in 1959 by the Home Office and the Ministry of Health, to "review existing laws and collect evidence from interested parties".[206] According to Harrison, the working party's report was not published but its proposals were made known to the "professions" via confidential memoranda.[207]

It is argued by the Author of this thesis that the impetus for change in the regulation of medicinal products did not occur until 1961, when thalidomide exposed the inadequacy of the existing legislation and became "the foundation stone on which the Medicines Act was built".[208] Stewart remarked that:

> " The thalidomide tragedy marked a turning; the end of innocence in drug therapy. No longer could a drug be used with the 'hope' that it would produce more benefit than harm. The tragedy marked the birth of a new, greater sense of responsibility in pharmacology, clinical testing of drugs and medicolegal relations." [209]

In 1963, during a parliamentary debate on the National Health Service, the shadow Health Secretary, Kenneth Robinson, commented:

> " The House and the public suddenly woke up to the fact that any drug manufacturer could market any product however inadequately tested, however dangerous, without having to satisfy any independent body as to its efficacy or its safety, and the public was almost uniquely unprotected in this respect." [210]

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[205] Ibid p122. See also Hodges and Appelbe (1987b).
[206] Harrison (1986a) p8.
[207] Ibid.
[208] Penn (1979), p303.
[209] Stewart, R.B. (1985) p33.
[210] Official Report, 5th Series, Commons, vol. 677 (8 May 1963), col.448. Robinson later became Minister of Health when the Labour party came to power in 1964.

In response to thalidomide, the Standing Medical Advisory Committees of England and Wales, and Scotland set up a Joint Sub-Committee on Safety of Drugs in August 1962, under the chairmanship of Lord Cohen of Birkenhead, with the following terms of reference:

> " To advise the Minister of Health and the Secretary of State for Scotland on what measures are needed:
>
> (i) to secure adequate pharmacological and safety testing and clinical trials of new drugs before their release for general use;
>
> (ii) to secure early detection of adverse effects arising after their release for general use;
>
> (iii) to keep doctors informed of the experience of such drugs in clinical practice." [211]

In November, the Joint Sub-Committee decided to issue three interim recommendations, because of the "widespread public concern":[212]

> " (1) The responsibility for the experimental laboratory testing of new drugs before they are used in clinical trials should remain with the individual pharmaceutical manufacturer.
>
> (2) It is neither desirable nor practicable that at this stage of their evaluation the responsibility for testing drugs should be transferred to a central authority.
>
> (3) There should be an expert body to review the evidence and offer advice on the toxicity of new drugs, whether manufactured in Great Britain or abroad, before they are used in clinical trials. The Sub-Committee proposed, in the light of further consideration and consultations, to formulate detailed advice on the composition and terms of reference of this advisory body." [213]

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[211]Joint Sub-Committee of the Standing Medical Advisory Committees (1963) p.5.
[212]Ibid.
[213]Ibid.

The Government accepted the first two recommendations immediately, but decided to wait for more details in the finished report before accepting the third recommendation.[214]

In March 1963, the Joint Sub-Committee published its full report and commented that the pharmaceutical industry discharged its responsibilities

> " effectively within the limits of existing knowledge of methods of testing. Public and professional opinion will, nevertheless, demand some type of formal machinery, independent of that of the manufacturer, for the assessment of the safety of a drug in relation to the purpose for which it is to be used. We do not think that this warrants any elaborate or large-scale system of control." [215]

In its report, the Joint Sub-Committee suggested that a voluntary scheme of regulation should be set up and administered by a Committee on Safety of Drugs, the expert body mentioned in its earlier interim recommendation. The Joint Sub-Committee also suggested that the Committee on Safety of Drugs should have three sub-committees to advise it on "the three clearly defined stages in the testing of a new drug":

> " (i) Toxicity tests on animals, and possibly on human volunteers, before a drug, which is thought to be promising pharmacologically, is used in clinical trials.
>
> (ii) Clinical trials designed to test efficacy; to establish the best formulation and dosage; to confirm that there are no short-term, unacceptable side-effects (careful attention should be paid to risks for special groups such as pregnant women); and to determine whether a drug is habit-forming.
>
> (iii) General release, during which other adverse reactions might begin to appear, possibly not before several years had elapsed." [216]

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[214] Ibid.
[215] Ibid. p6.
[216] Ibid. p7.

The Joint Sub-Committee acknowledged that a voluntary scheme could have no formal legal sanctions but suggested that prescribers should be informed by the Health Ministers if a manufacturer had ignored the advice of the Committee on Safety of Drugs, regarding the testing or marketing of a medicinal product.[217]

The only pharmacist members of the Joint Sub-Committee, John Grosset and Sir Hugh Linstead, disagreed with the Report's recommendations:

> " We believe that any voluntary system must have so many loopholes that it can offer no real additional safeguards to the public. In consequence we consider that there is no satisfactory alternative to early legislation." [218]

Specifically, they were concerned with the voluntary scheme being dependent on the co-operation of all of the pharmaceutical industry, the sanctions being few and weak, and the scheme giving the "appearance of safety without the reality".[219] They commented:

> " We know of no other countries comparable in their scientific and industrial development with our own that have not found it necessary to control drugs by statute." [220]

They also identified eight omissions of features in the voluntary scheme which they felt were "essential to the proper control of drugs".[221]

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[217]Ibid. pp9-10.
[218]Ibid. p12.
[219]Ibid.
[220]Ibid.
[221] " (a) It is almost certainly desirable that all new drugs should be restricted to medical prescription at least until their safety has been proved beyond question;
(b) There are some drugs (not necessarily poisons in the legal sense of the term) that the public should at no time be able to obtain except on production of a medical prescription;
(c) It is important that, whoever markets it, a drug shall always be called by the same name, preferably an internationally or nationally approved name, even when a trade name is also used;
(d) There are labelling requirements which ought to be imposed for the proper protection of the public, for example, a date after which a drug should not be used or a warning about possible dangers;
(e) Under a voluntary scheme a drug may be approved for one therapeutic purpose and later recommended by the makers for another. No voluntary scheme can control the therapeutic advice given to the medical profession about a new drug.
(f) There is no machinery for the continued oversight of drugs after they have been approved. For quite valid reasons their formulation may be changed or they may be combined with new ingredients.

However, the other members of the Joint Sub-Committee had recognised the urgent need for legislation and stated that the voluntary scheme was only an interim measure, which would not preclude the introduction of legislation.[222] They also mentioned a number of safety issues, outside their terms of reference, which they felt required some form of legislation. These issues included labelling, the control of the quality of medicinal products, the use of approved names and the over-the-counter sale of medicinal products. They concluded that the preparation of new legislation would involve "a comprehensive review of the whole field" and that this would be "a major undertaking".[223] During a Parliamentary debate, which discussed this report, shadow Health Secretary Kenneth Robinson pointed out that the inter-departmental working party, set up in 1959 by the Home Office and the Ministry of Health, had already completed a comprehensive review of this area and he criticised the Government for not yet having a Bill in draft.[224]

Despite these dissensions, the Ministers of Health accepted the Joint Sub-Committee's proposals for a voluntary scheme and, in June 1963, the Committee on Safety of Drugs was established.

3.5.2 The Committee on Safety of Drugs

On 1 January 1964, the Committee on Safety of Drugs (CSD) commenced full operation and continued working until September 1971. Its terms of reference were:

" 1. To invite from the manufacturer or other person developing or proposing to market a drug in the United Kingdom any reports they may think fit on the toxicity tests carried out on it; to consider whether any further tests should be

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(g) Except in the case of "therapeutic substances" and "dangerous drugs" there is no control over manufacture; and
(h) There are defects in the present statutory provisions for ensuring that drugs are adequately packed by manufacturers so as to guard against deterioration." Ibid. p13.

[222]Ibid p6.
[223]Ibid.

made, and whether the drug should be submitted to clinical trials; and to convey their advice to those who submitted reports.

2. To obtain reports of clinical trials submitted thereto.
3. Taking into account the safety and efficacy of each drug and the purposes for which it is to be used, to consider whether it may be released for marketing, with or without precautions or restrictions on its use; and to convey their advice to those who submitted reports.
4. To give manufacturers and others concerned any general advice they may think fit on the matters referred to in paragraphs 1-3.
5. To assemble and assess reports about adverse effects of drugs in use and prepare information thereon which may be brought to the notice of doctors and others concerned.
6. To advise the appointing Ministers on any of the above matters." [225]

Initially, the CSD was assisted by three sub-committees: the Sub-Committee on Toxicity; the Sub-Committee on Clinical Trials and Therapeutic Efficacy; and the Sub-Committee on Adverse Reactions. In 1967, the Sub-Committee on Toxicity and the Sub-Committee on Clinical Trials and Therapeutic Efficacy merged because of an overlap of functions.[226]

The first chairman of the CSD, Sir Derrick Dunlop, explained how the Committee operated:

" Despite the complete absence of legal sanctions the Association of the British Pharmaceutical Industry and the Proprietary Association of Great Britain, in the somewhat emotional atmosphere of the time, were quite glad to share some of the responsibility for the safety of their products with an independent body and promised before the Committee started to function on 1 January 1964 that none of their members would (a) submit for clinical trial or (b) market a new drug without

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[224]Official Report, 5th Series, Commons, vol. 677 (8 May 1963), col.450.
[225]CSD (1965a) p10.

> the Committee's approval - a promise loyally observed. The Committee attempted to solve its problems with the industry by voluntary compliance and mutual amplification or clarification, took place in robust but usually good natured encounters over the telephone or in informal meetings rather than in official communications. Manufacturers seemed to appreciate this informal approach." [227]

From 1964 to 1971, there were only three instances where the CSD had to report to the Health Ministers that a company was marketing products which had not been approved by the Committee.[228]

The work of the CSD is detailed in its annual reports; Table 16 lists the number of marketing and clinical trial applications which were received by the CSD.[229]

Table 16 Submissions for Medicinal Products Received by the CSD (1964-1971).

	1964	1965	1966	1967	1968	1969	1970	1971
Marketing Applications (* also includes Clinical Trial Applications)	600*	874*	705	563	552	630	536	432
Clinical Trial Applications	-	-	203	202	239	218	178	122

In this 8 year period, a total of 6054 applications were received: 4935 applications were approved, 254 applications were not approved and 621 were "withdrawn or not proceeded with". When the voluntary scheme ceased to operate, there were 244 applications still awaiting consideration.[230] Mann examined the above statistics in

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[226]CSD (1969a).
[227]Dunlop (1980) p.405. Mann (1984) p617 and Lancet (1971b) discuss Dunlop's personal contribution to the CSD. See also Cone (1988) for further background on the operation of the CSD.
[228]CSD (1968a), CSD (1969a) and CSD (1971).
[229]See CSD (1965a), (1966a), (1967a), (1968a), (1969a), (1971) and CSM (1972a) for further details.
[230]These outstanding applications had to be converted to applications for product licences or clinical trial certificates and submitted to the CSD's successor, the Committee on Safety of Medicines in order to comply with the requirements of the Medicines Act 1968.

detail and commented on the significance of the number of applications which were not approved by the CSD:

> " Unless the Dunlop Committee was grossly over-cautious (and its handling of drug problems once drugs had been marketed does not suggest that it was) it must be assumed that these refusals not only protected the public but establish that an external drug regulatory scheme is essential." [231]

Dunlop explained more fully the role of the CSD in relation to the consideration of marketing and clinical trial applications:

> " Rejections of new medicines were relatively few and constituted a comparatively minor part of the Committee's function. More important was the persuasion of manufacturers to alter their intentions, to modify their promotional claims or to issue warnings to doctors, when a medicine seemed to be developing undue or unexpected adverse reactions. In addition, the mere existence of the Committee may have tightened up standards." [232]

In 1964, the Committee started to develop a new system to study adverse reactions to medicinal products. An essential part of this system was the compilation of a register of adverse reactions. After consulting the British Medical Association, the CSD wrote to all dentists and doctors to tell them about the new system and give them a set of reply paid cards ("yellow cards"), which they could use to send in reports of any suspected adverse reaction.[233] The new reporting system went into full operation in 1965 and Table 17 details the number of adverse reaction reports received by the CSD from 1965 to 1971.

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[231]Mann (1984) p623.
[232]Dunlop (1980) p406.
[233]CSD (1965a).

Table 17 Reports of Adverse Reactions Received by the CSD (1965 - 1971).

Year	1965	1966	1967	1968	1969	1970	1971
Reports of Adverse Reactions Received	4,000	2,600	3,500	3,446	4,463	3,601	2,837

In its annual reports, the CSD expressed its disappointment at the "gross under-reporting" of adverse reactions.[234] In 1971, the Committee decided to introduce a new format of yellow card, which had stimulated adverse reaction reporting in a pilot scheme.[235] The introduction of the "yellow card" reporting scheme must be regarded as the most important achievement of the CSD. The scheme is still in use and one of its developers, Professor Inman, described it as:

> " The first line of defence in the detection and investigation of previously unsuspected adverse drug reactions. Yellow cards are instantly available from the moment a new drug is marketed and they have, over the years, brought to light many potentially serious problems." [236]

The CSD also issued information about potential safety problems involving medicinal products via Dear Doctor letters and Adverse Reaction Series leaflets (see Appendix VIII).

On several occasions, the Committee commented on areas where it had little or no control: the labelling of medicinal products;[237] the review of medicinal products on the market before 1964;[238] and the consideration of the efficacy of medicinal products.[239] The Committee always viewed itself as a "purely voluntary interim arrangement" [240] and acknowledged the need for legislation to replace the voluntary arrangements:

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[234]For example, CSD (1968a).
[235]CSM (1971).
[236]Drug Surveillance Research Unit (1983) p1.
[237]CSD (1969).
[238]CSD (1968).
[239]CSD (1967).
[240]Dunlop (1980).

" Whilst it appears to the Committee that in meeting their responsibilities for the safety of drugs they have not been hampered in any way by lack of statutory powers, largely due to the co-operation of manufacturers, they believe that the arrangements ought to be given permanence within the framework of legislation." [241]

3.5.3 Introduction and Structure of the Medicines Act 1968

" Will some clever person please explain to me what is the purpose of the new Medicines Act, apart from finding employment for swarms of lawyers and civil servants?" [242]

In September 1967, the White Paper, "Forthcoming Legislation on the Safety, Quality and Description of Drugs and Medicines", was published.[243] This White Paper reiterated the need for legislation which the Joint Sub-Committee had voiced in 1963 and the Committee on Safety of Drugs had voiced in 1965 and stated:

" The voluntary system has had the full support of the pharmaceutical industry and the medical and pharmaceutical professions, but the Government considers that the provision of statutory backing for these safeguards would give greater reassurance and should not be further delayed." [244]

It was proposed that legislation would apply throughout the United Kingdom to medicinal products and devices for both human and veterinary use, and would contribute to consumer protection in two respects:

" First, it will improve the provisions designed to secure that the product supplied to the customer is what he asked for and that he is not misled by description and labelling of the product or unsupported therapeutic claims; and second, it will ensure so far as possible that the professions can rely on the purity and efficacy of

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[241]CSD (1966) p15.
[242]Hayhurst (1971).
[243]Cmnd 3395 (London, HMSO, 1967).

> the substances that they prescribe, supply and use in treating disease in man and animals, and be fully informed about the properties, desirable and undesirable, of these substances, so that they can exercise their professional judgement in the light of this knowledge." [245]

The White Paper outlined plans for a licensing system to control the safety, quality and efficacy of medicinal products. It was proposed that the licensing system would be under the control of the Health and Agriculture Ministers and would regulate clinical trials, manufacture, marketing, importation and wholesale dealing. Other proposals included the setting up of a Medicines Commission and other expert committees, and measures to control the retail sale and supply of medicinal products.

On 2 February 1968, the Medicines Bill (based on the proposals of the White Paper) began its passage through Parliament and received the Royal Assent on 25 October 1968.[246] A series of transitional exemptions and commencement orders marked the gradual introduction of the Act.[247] The Act is divided into eight parts: "Administration"; "Licences and Certificates relating to Medicinal Products"; "Further Provisions relating to Dealings with Medicinal Products"; "Pharmacies"; "Containers, Packages and Identification of Medicinal Products"; "Promotion of Sales of Medicinal Products"; "British Pharmacopoeia and Other Publications"; and "Miscellaneous and Supplementary Provisions". The Act consists of 136 sections and 8 schedules; over 300 statutory instruments have revoked, amended or supplemented these provisions, including, in particular, the 1994 Regulations

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[244]Ibid. p2.
[245]Ibid. p3.
[246]Presented and First Reading (Kenneth Robinson) Official Report, 5th Series, Commons, vol. 757 (2 February 1968) col. 1713; Second Reading and committed to a Standing Committee, vol. 758 (15 February 1968) col. 1600-711; Report, vol. 766 (20 June 1968) col. 1382-456; Report, vol. 767 (24 June 1968) col. 52-110; Third Reading, vol. 767 (24 June 1968) col. 111; Lords Amendments considered, vol. 770 (18 October 1968) col. 772-839; Royal Assent, vol. 770 (25 October 1968) col. 1729.
[247]For example, section 16 of the Medicines Act 1968 (transitional exemptions) and The Medicines Act 1968 (Commencement No. 1) Order 1972. [S.I. No.788]. The Act is not yet fully operational: section 48, "postponement of restrictions in relation to exports", and parts of section 135 relating to "minor and consequential amendments and repeals", have not been brought into force.

mentioned earlier. Appendix XI gives a full outline of the provisions of the Act and Appendix III gives a full list of statutory instruments pertaining to medicinal products for human use.[248]

The Medicines Act 1968 applied to "medicinal products"; the terms "medicines" or "drugs" are not used. The definition of "medicinal product" was described by a former Minister of Health, Kenneth Robinson, as being "rather long and complicated". Mr Robinson also commented:

> " The definition has not been easy to draft in such a way as to avoid too wide a definition - by bringing in any substance capable of medicinal use - or too uncertain a definition - for example, by making it dependent on evidence of actual use of the substance in question - or too limited - for example, by linking it with a specific recommendation for the treatment of a particular disease or condition."
> [249]

Section 130 of the Medicines Act 1968 defined a "medicinal product" as being

> " any substance or article (not being an instrument, apparatus or appliance) which is manufactured, sold, supplied, imported or exported for use wholly or mainly in either or both of the following ways, that is to say -
>
> (a) use by being administered[250] to one or more human beings or animals for a medicinal purpose;[251]

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[248] For further information on the provisions of the Act, see, in particular, Harrison (1986a, 1986b and 1986c) and Appelbe and Wingfield (1997), who have conducted very detailed studies of the Act. Other authors such as Pharmaceutical Journal (1972), "The British System of Drug Regulation" in Landau, ed. (1973), Teff (1984), Andrews et al (1984), "The Regulation of Medicines in the UK", in Burley and Binns,eds. (1985), McCall Smith (1988), Medicines Division (1988g), Watt (1990), Stewart (1991), Chapter 17 in Cartwright and Matthews (1991)"Medicines Control within the United Kingdom", in Griffin, ed. (1992) and MCA (1993g) have also produced overviews of the operation of the Act.

[249] Official Report, 5th Series, Commons, vol. 758 (5 February 1968) col.1607. These comments were made during the Second Reading of the Medicines Bill.

[250] Section 130(9) defines "administer" as meaning "administer to a human being or animal, whether orally, by injection or by introduction into the body in any other way, or by external application, whether by direct contact with the body or not; and any reference in this Act to administering a substance or article is a reference to administering it either in its existing state or after it has been dissolved or dispersed in, or diluted or mixed with, some other substance used as a vehicle."

[251] " (a) treating or preventing disease;
(b) diagnosing disease or ascertaining the existence , degree or extent of a physiological condition;
(c) contraception

(b) use, in circumstances to which this paragraph applies,[252] as an ingredient in the preparation of a substance or article which is administered to one or more human beings or animals for a medicinal purpose."[253]

Section 130(4) and (5) of the Act specifically excluded certain items from the definition of "medicinal product".[254]

Ministers used section 104 of the Act to extend the application of the Act to include any articles or substances which are not medicinal products but are manufactured, sold, supplied, imported or exported for a medicinal purpose. Orders have included: certain types of surgical ligatures, sutures and other surgical materials;[255] dental filling substances;[256] contact lenses, solutions, and intrauterine contraceptive devices;[257] radioactive substances;[258] and cyanogenetic substances.[259] Section 105 was also used by Ministers to extend the application of the Act to:

(d) inducing anaesthesia
(e) otherwise preventing or interfering with the normal operation of a physiological function, whether permanently or temporarily, and whether by way of terminating, reducing or postponing, or increasing or accelerating, the operation of that function or in any other way." Section 130(2)

[252] " (a) use in a pharmacy or in a hospital;
(b) use by a practitioner;
(c) use in the course of a business which consists of or includes the retail sale, or the supply in circumstances corresponding to the retail sale, of herbal remedies." Section 130(3).

[253] Section 130(1)

[254] " any substance or article which is manufactured for use wholly or mainly by being administered to one or more human beings or animals, where it is to be administered to them
(a) in the course of the business of the person who manufactured it (in this subsection referred to as "the manufacturer"), or on behalf of the manufacturer in the course of the business of a laboratory or research establishment carried on by another person, and
(b) solely by way of a test for ascertaining what effects it has when so administered, and
(c) in circumstances where the manufacturer has no knowledge of any evidence that those effects are likely to be beneficial to those human beings, or beneficial to, or otherwise advantageous in relation to those animals, as the case may be,
and which (having been so manufactured) is not sold, supplied or exported for use wholly or mainly in any way not fulfilling all the conditions specified in paragraphs (a) to (c) of this subsection." Section 130(4)
Section 130 (5) excludes:
(a) substances used in dental surgery for filling dental cavities;
(b) bandages and other surgical dressings, except medicated dressings where the medication has a curative function which is not limited to sterilising the dressing;
(c) substances and articles of such other descriptions or classes as may be specified by an order made by the Ministers, the Health Ministers or the Agriculture Ministers for the purposes of this subsection."

[255] The Medicines (Surgical Materials) Order 1971. [S.I. No. 1267].

[256] The Medicines (Dental Filling Substances) Order 1975. [S.I. No. 533]. This amends the exclusion in section 130(5)(a).

[257] The Medicines (Specified Articles and Substances) Order 1976. [S.I. No. 968].

[258] The Medicines (Radioactive Substances) Order 1978. [S.I. No. 1004].

" a substance which is not itself a medicinal product but -

(a) is used as an ingredient in the manufacture of medicinal products, or

(b) if used without proper safeguards, is capable of causing danger to the health of the community, or of causing danger to the health of animals generally or of one or more species of animals." [260]

Orders have included: biological substances;[261] stilbenes and thyrostatic substances;[262] and antimicrobial substances.[263] Harrison explained the reason why biological substances have been controlled by the Medicines Act:

" Normally substances used as ingredients in the manufacture of various medicinal products are not regarded as medicinal products because their specifications can be strictly controlled in the product licences. The substances mentioned here are not capable of being adequately tested by chemical means, and for this reason their manufacture was controlled under the Therapeutic Substances Act. The same considerations still apply, hence they were brought within the scope of the Act to ensure that their manufacture, labelling, and all dealings therein are now subject to control." [264]

On 1 September 1971, "the first appointed day", the licensing provisions of the Medicines Act 1968 came into force.[265] These provisions introduced product licences, manufacturers' licences, wholesale dealers' licences and clinical trial certificates. In its first annual report, the Medicines Commission admitted to feeling

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[259]The Medicines (Cyanogenetic Substances) Order 1984 [S.I. No. 187]. Harrison explains that these substances are controlled because they were used in the treatment of cancer and there was no evidence of any benefit. There was, however, evidence of toxicity and adverse reactions. (Harrison (1986a p42).

[260]Section 105(1).

[261]The Medicines (Control of Substances for Manufacture) Order 1971 [S.I. No. 1200] and The Medicines (Control of Substances for Manufacture) Order 1985 [S.I. No. 1403. Both amended by The Medicines (Control of Substances for Manufacture and Exportation of Specified Products for Human Use) Amendment Order 1994 [S.I. No. 787] to apply only to substances for veterinary use

[262]The Medicines (Control of Substances for Manufacture) Order 1982 [S.I. No. 425]. Applies to substances for veterinary use.

[263]The Medicines (Extension to Antimicrobial Substances) Order 1973. [S.I. No. 367].

[264]Harrison (1986a) p42.

[265]The Medicines (First Appointed Day) Order 1971. [S.I. No. 1153]. Specifically, sections 7 and 8.

impatient at the time it was taking to introduce the Act's licensing provisions. This was attributed to the

> " vast amount of preparatory work and the considerable extent of consultation in matters of detail which are necessary." [266]

Harrison commented on the significance of these new provisions:

> " The licensing system is the chief novel feature of the Act, and lies at the heart of all of the control over medicines. The system is designed to ensure that medicinal products (and certain other substances and articles) are of good quality, safe and efficacious and are manufactured and dealt with under optimal conditions."[267]

Part II of the Act "Licences and Certificates relating to Medicinal Products" sets out the framework of the licensing system and includes provisions relating to the grant, refusal, appeal, duration, renewal, variation, suspension and revocation of the various licences and certificates.[268] Sections 9 to 14 of the Act have set out various

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[266]Medicines Commission (1971) p.9.

[267]Harrison (1986a) p45. Harrison further commented on the benefits of operating such a system:
" A licensing system is ideal for controlling such a complex and technical field as the manufacture and testing of medicinal products for the following reasons -
(1) It is flexible, a person can be licensed to do one thing or many things;
(2) A licence can be tailored to meet exactly the applicant's needs;
(3) A licence can subsequently be varied to take account of major changes in the specifications of the product or of its use;
(4) A licence can be issued subject to conditions, and acceptance of the licence means acceptance of the conditions. One of the standard conditions of all licences requires the licensee to notify the authority of every change which might affect the safety, quality or efficacy of the product;
(5) If a licensee fails to comply with the terms and/or conditions of the licence, the licence can be suspended or even revoked, and while the licensing authority cannot act in an arbitrary manner, they do not have to satisfy a judge and jury of the correctness of their decision;
(6) A licence lasts for a fixed time (usually 5 years) and at its expiry it can be reviewed and renewed if desired;
(7) The licence has to be paid for and consequently the costs of the system are largely borne by the licence-holders (in fact, the fees are now set with the intention of fully covering the costs of the system)." Ibid p47.
Harrison suggested that at least one disadvantage of this system was the cost of the licence fees and the cost of producing the "necessary paperwork". Ibid.

[268] Several "Medicines Act Leaflets" (MALs) have provided guidance on these various licensing procedures: "Guide to the Licensing System" [MCA (1988)]; "Guidance Notes on Applications for Product Licences" [MCA (1989a)]; "Hearings and Representations under Part II of the Medicines Act 1968" [Medicines Division (1984b)]; "Notes on Applications for Product Licences (Parallel Importing)(Medicines for Human Use) [Medicines Division (1987a)]; "Notes on Applications for a Manufacturer's Licence" [MCA (1990b)]; "Notes on Applications for a Wholesale Dealer's Licence" [Medicines Division (1988g)]; "Guidance Notes on Applications for Clinical Trial Certificates and Clinical Trial Exemptions" [Medicines Division (1984a) and Supplement (1985a)]; and "New Applications Regulations and Amendments to Standard Provisions Regulations (Product Licences for Products for Human Use)" [MCA (1993l)]. See also Appelbe and Wingfield (1997), Harrison (1986a), MCA (1993g), Watt (1990), Chapter 17 in Cartwright and Matthews (1991) and Chapter 1 in Griffin, ed. (1992).

exemptions from the requirements to hold licences or certificates; various statutory instruments have extended or modified these exemptions in terms of sections 13(2) and 15(1) of the Act.[269] Exemptions have covered: doctors and dentists;[270] pharmacists;[271] nurses and midwives;[272] herbal remedies;[273] imports;[274] re-exports;[275] foods and cosmetics;[276] "special manufactured products";[277]exports;[278] wholesalers;[279]confectionery;[280] ingredients;[281] osteopaths, chiropodists and naturopaths;[282] clinical trials;[283] and radiopharmaceuticals.[284]

The most important provision in Part II of the Act is section 19 which sets out three factors which should be taken into account in relation to applications for product licences:

> " (a) the safety of medicinal products of each description to which the application relates;
>
> (b) the efficacy of medicinal products of each such description for the purposes for which the products are proposed to be administered; and
>
> (c) the quality of medicinal products of each such description, according to the specification and the method or proposed method of manufacture, and the provisions proposed for securing that the products as sold or supplied will be of that quality." [285]

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[269]See Appelbe and Wingfield (1997) for fuller details.
[270]Section 9.
[271]Section 10 and S.I. 1971/1445.
[272]Section 11.
[273]Section 12.
[274]Section 13, S.I. 1974/316, S.I. 1978/ 1461, S.I. 673
[275]Section 14.
[276]S.I. 1971/1410 and S.I. 1973/2079.
[277]S.I. 1971/1450, S.I. 1972/1200, S.I. 1989/1184 and S.I. 1989/2323,
[278]S.I. 1971/1198.
[279]S.I. 1972/640, S.I. 1977/1054, S.I. 1983/1728, S.I. 1989/2322 and S.I. 1990/566.
[280]S.I. 1975/762.
[281]S.I. 1974/1150.
[282]S.I. 1979/1114.
[283]S.I. 1974/498, S.I. 1981/164, S.I. 1995/2808 and S.I. 1995/2809.
[284]S.I. 1992/2844.
[285]Section 19(1).

Section 19 further states that, when considering the efficacy of a medicinal product:

> " The Licensing Authority shall leave out of account any question whether medicinal products of another description would or might be equally or more efficacious for that purpose. Provided that nothing in this subsection shall be construed as requiring the Licensing Authority, in considering the safety of medicinal products of a particular description, in relation to a purpose for which they are proposed to be administered, to leave out of account any question whether medicinal products of another description, being equally or more efficacious for that purpose, would or might be safer in relation to that purpose.'[286]

This provision has not been revoked by the 1994 Regulations.

Section 45 of the Act sets out offences under Part II (Licensing) of the Act.

- any person who contravenes any of the provisions of section 7 [product licences], section 8 [wholesale dealer's and manufacturer's licences] and section 31 [clinical trial certificates] or who is in possession of any medicinal product for the purpose of selling, supplying or exporting it in contravention of any of those sections, shall be guilty of an offence.[287]

- where any medicinal product is imported in contravention of section 7, any person who, otherwise than for the purpose of performing or exercising a duty or power imposed or conferred by or under the Act or any other enactment, is in possession of the product knowing or having reasonable cause to suspect that it was so imported shall be guilty of an offence.[288]

- any person who, being the holder of a product licence or of a clinical trial certificate, procures another person to carry out a process in the manufacture or assembly of medicinal products of a description to which the licence or certificates relates, and (a) does not communicate to that person the provisions of the licence or certificate which are applicable to medicinal products of

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[286]Section 19(2).
[287]Section 45(1).

> that description, or (b) in a case where any of those provisions has been varied by a decision of the Licensing Authority, does not communicate the variation to that person within fourteen days after notice of the decision has been served on him, shall be guilty of an offence.[289]

Information on successful prosecutions brought by the Department of Health is published in the MAIL (Medicines Act Information Letter) series. The Author examined every issue from 1973 until July/August 1997 to compile a list of successful prosecutions for offences related to product licences, manufacturers' licences and wholesale dealers' licences. Reports of decisions by the Statutory Committee of the Royal Pharmaceutical Society which related to licensing prosecutions and which were published in The Pharmaceutical Journal, were also consulted. Prosecutions relating to other offences are discussed in Chapter Four.[290] The prosecutions related to licensing offences are listed in Appendix XII. In general terms, the Author would argue that the fines related to these prosecutions were too low, considering the potential seriousness of these offences.

3.5.4 Administration of the Regulatory Scheme

Under the Act, section 1 states that the "Health Ministers"[291] and the "Agriculture Ministers"[292] are responsible for the administration of the Medicines Act.[293]. This provision is repeated in the 1994 Regulations.[294] However, the "day to day responsibilities of medicines control" have been and continue to be delegated by Ministers to the Medicines Control Agency (MCA).[295] Formerly, these

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[288]Section 45(2).
[289]Section 45(3). Section 46 sets out "special defences" to these offences.
[290] p244.
[291]The Minister of Health, the Secretary of State concerned with health in Scotland and the Minister of Health and Social Services for Northern Ireland. Section 1(1)(a).
[292]The Minister of Agriculture, Fisheries and Food, the Secretary of State concerned with agriculture in Scotland and the Minister of Agriculture for Northern Ireland. Section 1(1)(b).
[293]Section 1 also explains that sometimes the Health and Agriculture Ministers will act together, but, in relation to medicinal products for human use, the Health Ministers, unless specified, act alone.
[294] Paragraph 2, SI No. 3144
[295]MCA (1994)

responsibilities were delegated to the Medicines Division of the Department of Health and Social Security. The MCA is described as:

> " the executive arm of Government which regulates the pharmaceutical sector and implements policy in this area."[296]

Section 2 of the Act established the Medicines Commission, a group of independent experts, to advise the Ministers:

> " On matters relating to the execution of this Act or the exercise of any power conferred by it, or otherwise relating to medicinal products, where either the Commission consider it expedient, or they are requested by the Minister or Ministers in question to do so." [297]

Following a recommendation from the Medicines Commission, section 4 of the Act enables the Ministers to establish other committees:

> " For any purpose, or combination of purposes, connected with the execution of the Act or the exercise of any power conferred by it, either generally or in relation to any particular class of substances or articles to which any provision of this Act is applicable."[298]

Since 1970, the Ministers have used this section to establish the following seven committees : the Committee on Safety of Medicines,[299] the British Pharmacopocia Commission,[300] the Veterinary Products Committee,[301] the Committee on the Review

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[296]MCA (1993g) p19.
[297]Section 3(1).
[298]Section 4(2).
[299]The Medicines (Committee on Safety of Medicines) Order 1970. [S.I. No. 1257]. A recommendation to establish a Committee to give advice regarding quality, safety and efficacy, and the collection and investigation of information relating to adverse reactions is contained in Section 4(3) of the Act.
[300]The Medicines (British Pharmacopoeia Commission) Order 1970. [S.I. No. 1256]. A recommendation to establish a Committee concerned with the British Pharmacopoeia is contained in section 4(4) of the Act.
[301]The Medicines (Veterinary Products Committee) Order 1970. [S.I. No. 1304]. The Committee was established for the following purposes:
"(a) giving advice with respect to safety, quality and efficacy in relation to the veterinary use of any substance or article (not being an instrument, apparatus or appliance) to which any provision of the Medicines Act is applicable.
(b) promoting the collection of information relating to suspected adverse reactions for the purpose of enabling such advice to be given."
It is not proposed to examine the work of this committee, as veterinary products are not discussed by this thesis.

of Medicines,[302] the Committee on Dental and Surgical Materials,[303] the Committee on Radiation from Radioactive Products[304] and the Advisory Board on the Registration of Homeopathic Medicinal Products.[305] The 1994 Regulations have not affected the operation of the Medicines Commission, the Committee on Safety of Medicines, the British Pharmacopoeia Commission, the Veterinary Products Committee and the Advisory Board on the Registration of Homeopathic Medicinal Products.

The Ministers appoint the members and chairmen of the Medicines Commission and the "section four committees".[306] Schedule 1 of the Act contains supplementary provisions relating to the Commission and Committees, including: the power of Ministers to make regulations regarding the terms of office and appointment of members, and also the establishment of sub-committees;[307] procedure at meetings, the supply of accommodation, staff and services; vacancies; remuneration; the payment of expenses; and Crown immunity.

In Sections A to F, the Author discusses the work of Medicines Division, the Medicines Control Agency, the Medicines Commission, the Committee on Safety of Medicines, the British Pharmacopoeia Commission, the Committee on Dental and Surgical Materials and the Committee on the Review of Medicines. This provides a comprehensive view of how the Medicines Act 1968 has operated in practice and

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[302]The Medicines (Committee on the Review of Medicines) Order 1975. [S.I. No. 1006]
[303]The Medicines (Committee on Dental and Surgical Materials) Order 1975. [S.I. No. 1473].
[304]This Committee was established by The Medicines (Committee on Radiation from Radioactive Products) Order 1978. [S.I.1005]. Its terms of reference were:
"To give advice with respect to the safety, quality and efficacy, in relation to radiation, of any substance or article for human use to which any provision of the Medicines Act 1968 is applicable. Thus the Committee advises the licensing authority on the radiation aspects of medicinal products and applications for product licences or proposals to review, suspend, revoke or vary licences." [Medicines Commission et al (1980)].
The Medicines Commission recommended that the committee should be abolished because of its small workload [Medicines Commission et al (1985) p3] and it was disbanded in 1984. [SI 1984/1261].
[305]The Medicines (Advisory Board on the Registration of Homeopathic Products) Order 1995. [S.I. No. 309].
[306]Sections 2(2), (4) and 4(5).
[307]See The Medicines Commission and Committees Regulations 1970. [S.I. No. 746].

provides an insight as to the manner most of these bodies will continue to operate under the 1994 Regulations.

A. The Medicines Division and the Medicines Control Agency

> " The Medicines Division of the Department of Health and Social Security is responsible for matters relating to the safety, quality and efficacy of medicines, including international aspects. The bulk of the work relates to responsibilities arising under the Medicines Act 1968. The Division provides professional and administrative support for the Medicines Commission and, with the exception of Veterinary Products Committee, which is a matter for the Ministry of Agriculture, Fisheries and Food, for the specialist bodies established under section 4 of the Act. [...] The Division also exercises the functions of the licensing authority under the Medicines Act in respect of human medicines, manufacturers' and wholesale dealers' licences for all types of medicinal product. In addition the Division is responsible for enforcement and inspection.[308]

Table 18 shows the numbers and types of licensing applications which were received by the Medicines Division in the period from 1973 until 1987.[309] In particular, this Table illustrates that there was a large rise in requests for licence variations and export certificates.

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[308]Medicines Commission et al (1979) p96.
[309]The statistics are based on the Annual Reports of Medicines Division from 1973 until 1978 [to be found in Medicines Commission et al (1974) to (1979)], and Evans and Cunliffe (1987).

Table 18 Licensing Applications received by the Medicines Division (1973 - 1987)

	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987
New Product Licences	514	704	623	762	660	835	922	1180	1043	1282	1158	922	1365	1217	1073
Product Licence Renewals	-	-	-	-	480	256	252	216	243	606	465	499	419	830	1294
Variations: Product Licences, Product Licences of Right and Clinical Trial Certificates [*includes product licence (parallel imports)]	1800	3300	3404	4788	3968	3945	5130	7007	7297	7384	5940	6421	7887*	8534*	10564*
Clinical Trial Certificates and CTC Renewal	194	138	144	123	224	260	214	296	177	211	155	121	107	94	97
Clinical Trial Exemption Certificates	-	-	-	-	-	-	-	-	208	232	252	263	233	249	217
Clinical Trial Exemption Certificates: variations and renewals	-	-	-	-	-	-	-	-	-	-	-	978	1500	2833	-
Manufacturers' Licences, Renewals and Variations [includes application from unorthodox practitioners]	137	62	532	227	777	91	124	118	290	780	481	609	683	739	939
Wholesale Dealers' Licences, Renewals and Variations	917	85	53	62	847	149	115	832	264	816	507	462	829	592	829
Product Licence (Parallel Imports)	-	-	-	-	-	-	-	-	-	-	-	1624	665	939	113
Export Certificates	1694	4336	4621	7921	7656	11181	11157	10948	12439	11389	11956	10903	12330	13380	12373

In acknowledgement of this large rise, in 1987, the Minister of Health, appointed Dr. N.J.B. Evans, previously a Deputy Chief Medical Officer, and Mr. P.W. Cunliffe, who was about to retire from the chairmanship of the pharmaceuticals division of ICI to:

> " **Examine the issues for DHSS arising from the continued increases in licence applications and other work under the Medicines Act and to recommend ways of dealing expeditiously with this work, while maintaining adequate standards for the safety, efficacy and quality of human medicines in the United Kingdom."** [310]

In preparing their report, Evans and Cunliffe examined the working of the Medicines Division, heard the views of sixty-three members of staff and sent out a letter to seek the views of various "interested parties". They received sixty-two written and oral replies from a selection of pharmaceutical companies (e.g. Ciba-Geigy, ICI and Glaxo), professional organisations (e.g. the British Institute of Regulatory Affairs (BIRA), the Association of the British Pharmaceutical Industry (ABPI), the Proprietary Association of Great Britain (PAGB), the Royal Pharmaceutical Society of Great Britain, the British Dental Association and the Royal College of General Practitioners), consumer organisations (e.g. Social Audit Ltd, the Consumers' Association and the Patients' Association) and members of the Medicines Commission and section 4 committees.[311]

In chapter three of their report, Evans and Cunliffe summarised the principal complaints and difficulties they uncovered from their research, which included the main complaint that the increase in the workload of Medicines Division had caused overload and delay.[312] They made fifty-four recommendations regarding organisation, new technology, staffing and personnel, the improvement of

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[310]Evans and Cunliffe (1987) p7.
[311] Ibid p45-46.
[312]Ibid p10-11.

procedures, adverse drug reaction reporting, the expert advisory committees, appeals and finance. They commented:

> " The heart of our recommendations is our proposal to organise the staff, of all disciplines, into functional teams each related to an identifiable 'business' and each with a team leader managerially responsible for the quality and quantity of its work. For example, there will be one team for New Active Substance applications, another for Adverse Drug Reaction monitoring, and so on. Team leaders will be accountable to functional managers headed by the Director of Medicines Control whose task will be to control the work and promote the identity of the Directorate." [313]

In April 1989, following these recommendations, Medicines Division was reorganised and replaced by the Medicines Control Agency. In July 1991, the MCA was established as an Executive Agency of the Department of Health under the Government's "Next Steps" initiative. The MCA was awarded this status in order to

> " meet the challenges of the future, using a number of new freedoms to manage and innovate, particularly in the financial and personnel fields" [314]

In 1993, the MCA achieved Trading Fund status and manages its own finances, principally income from licence fees.[315]

> The MCA operates within the terms of a "Framework Document", which sets out policy, planning, control, delegations and accountability. [316]

The MCA's main strategic objectives are to:

> " a) ensure through a system of licensing, classification, monitoring and enforcement that medicines sold or supplied in the UK for human use are of an acceptable standard of safety, quality and efficacy;

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[313] Ibid p 2.
[314] MCA (1992a) p10.
[315] The Medicines Control Agency Trading Fund Order 1993 [S.I. No. 751].
[316] MCA (1991b) p.5.

b) provide this service effectively without unnecessary impediment to the functioning of the pharmaceutical industry;

c) protect UK public health interests in relation to EC licensing and associated developments;

d) contribute effectively to the evolving European licensing arrangements;

e) discharge its responsibilities in an efficient and effective manner so that the licence and other fees are no higher than is necessary;

f) seek continual improvements in the quality, efficiency and effectiveness of its services, including meeting performance targets agreed with Ministers;

g) maintain and develop its worldwide reputation for excellence and high standards of regulatory decision making." [317]

Initially, the MCA was divided into a Finance Directorate and six multi-disciplinary businesses: New Drugs; Abridged Licensing; Pharmacovigilance; Inspection and Enforcement; Pharmacopoeia; and Executive Support. In 1991, the Pharmacopoeia Business was disbanded and its work split between the New Drugs and, Inspection and Enforcement Businesses.[318] In 1994, further reorganisation took place. It was considered that new arrangements for the licensing of medicinal products in the European Community, was

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[317]Ibid. The document further explains that the MCA will fulfil its objectives through:
"a) an effective and efficient system for the licensing and classification of medicines and the licensing of manufacturers and wholesale dealers, in accordance with the statutory requirements of the Medicines Act 1968 and EC Directives;
b) effective arrangements for the monitoring of adverse reactions to medicines and suspected defective medicines and timely action where necessary to remove or restrict the availability of medicines or promote safer use;
c) inspection and enforcement arrangements for the UK to ensure adherence by the industry to statutory requirements in respect of the manufacture, distribution, sale, labelling, advertising and promotion of medicines;
d) the UK contribution to the developing regulatory requirements for medicines within the EC ensuring that UK standards for the protection of public health are not put at risk, and representing UK interests in respect of regulatory matters in World Health Organisation (WHO) and other international settings;
e) promotion of and support for the publication of quality standards for medicines through the work of the British Pharmacopoeia Commission and by the support of UK interests in the European Pharmacopoeia." Ibid.

[318]MCA (1992a) p11.

> " an opportune moment to regroup within the organisation so that it is in the best possible shape to meet the challenges ahead." [319]

The MCA is now divided into: Licensing Division; Post-Licensing Division; Inspection and Enforcement; Executive Support; and Finance Directorate.

The Licensing Division deals with: applications for product licences/marketing authorizations; applications for abridged product licences; applications, adverse reactions and variations relating to clinical trials and the clinical trial exemption scheme; applications, variations and renewals relating to parallel import product licences; applications for homeopathic registration licences; applications for European marketing authorizations (centralised and decentralised procedures); and the preparation of the British Pharmacopoeia. The Licensing Division also provides administrative support to the Medicines Commission and the section four committees. The Post-Licensing Division is responsible for pharmacovigilance, product information, control of advertising, variations of product licences, renewals of product licences and the re-classification of the legal status of medicinal products. Inspection and Enforcement is responsible for applications and variations relating to Manufacturers' Licences, applications and variations relating to Wholesale Dealers' Licences, inspection of manufacturing and wholesaling sites, the Defect Medicines Report Centre, the MCA laboratory and the issue of export certificates. Executive Support provides the infrastructure for the other Divisions. It is also responsible for the policy for fees, information technology and the MCA Information Centre.[320]

Table 19 summarises the work of the MCA from 1990 to 1997. The information in this table is based on an analysis of the annual reports published by the MCA.[321]

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[319]MCA (1994e) p4.
[320]See MCA (1995j). More detailed information on the work of the MCA can be found in MCA (1992b), (1992i), (1993g), (1993j) and the annual reports of the MCA.
[321]See MCA (1991a), (1992a), (1993f)(1994g) and (1995j) for further details.

Unfortunately, the information featured in these reports was often presented in a confusing manner; references were made to "percentage increases" but the actual figures involved were not given, approximate figures were quoted and sometimes the graphs used were not clear. Therefore, this table can only be referred to as a rough guide to the activities of the MCA. A further analysis of the work of the MCA will be conducted in Chapter Four.[322] See also Appendix XIII for a summary of the MCA's "highlights and achievements" taken from the MCA's annual reports.

Table 19 An Analysis of the Work of the MCA (1990 - 1997)[323]

	1990/91	1991/92	1992/93	1993/94	1994/95	1995/96	1996/97
Product Licence/Marketing Authorization applications [*New Active Substances Only]	83*	51*	79*	1079	1252	1,099	1,147
Product Licence appeals	31	35	32	48	27	?	26
Product Licence variations	2,223	11,000	9,500	9,700	11,484	13,000+	15,000
Abridged Product Licence applications	1,622	711	823	1,164	684	1,136	1,126
Renewal applications	?	1,487	1,186	1,800	1,822	1,884	1,810
Parallel Import Licence applications	877	245	267	366	243	461	570
Clinical Trial Exemption (CTX) applications (new, abridged, variations and renewals)	2,560	2,916	3,106	3,668	3,639	3,412	2,601
Rapporteur in EC licensing applications	?	14	?	29	?	15	13
Manufacturer's Licence applications	41	154	32	72	53	57	30
Manufacturer's Licence variations	378	575	581	556	358	286	213
Wholesale Dealer's Licence applications	86	213	125	123	161	146	135

[322] For example, p215.
[323] The use of a question mark in this table indicates that precise details were not given, but that nevertheless the activity took place.

Table 19 contd.

	1990/91	1991/92	1992/93	1993/94	1994/95	1995/96	1996/97
Wholesale Dealer's Licence variations	157	225	301	277	254	315	203
Export Certificates	?	5,916	6,507	7,025	7,829	8,802	12,494
Homeopathic Registration Licences	-	-	-	-	30	?	?
Adverse drug reaction reports [UK and "Foreign"]	21,000	24,709	28,215	27,077	27,770	32,493	31,794
Product Licences varied for safety reasons	625	642	218	174	258	92	281
Reclassification of medicinal products (POM to P)	-	-	-	-	31	15	24
Reclassification of medicinal products (P to GSL)	-	-	-	-	21	16	35
Referrals to Borderline unit	-	-	-	-	-	1000+	1200
Product Licences withdrawn for safety reasons [*drug substances present in a number of product licences]	4	45	2*	2*	?	?	?
Enquiries on drug safety matters	1,800	2,373	2,500	4,064	4,162	4,234	4,527
Anonymised adverse drug reaction reports provided to the pharmaceutical industry	16,000	13,906	11,630	9,140	11,028	69,709	72,025
Patient Information Leaflet applications	667	430	452	?	?	?	?
Correspondence on labels, patient information leaflets and data sheets	406	496	504	?	?	?	?
Promotion Complaints and correspondence	242	230	184	?	?	?	41
New active substance advertisements scrutinised	-	247	216	?	?	?	100
Inspections of manufacturers' and wholesale dealers' premises	610	578	637	569	576	595	763

Table 19 contd.

	1990/91	1991/92	1992/93	1993/94	1994/95	1995/96	1996/97
Defective medicines reports	209	247	227	265	229	215	209
Products subjected to analytical quality examination	1,500	1580	1,100	1,554	2,002	2,427	2,909
Enforcement cases	207	140	117	164	?	?	234
Prosecutions	15	?	6	20	52	?	63

B. The Medicines Commission

The Medicines Commission was established in 1969 and its first chairman was the former chairman of the Committee on Safety of Drugs, Sir Derrick Dunlop.[324] The Act sets out various details regarding the membership of the Commission, stating that there must be at least eight members and that they must include at least one representative from the following "activities": medicine; veterinary medicine; pharmacy; chemistry other than pharmaceutical chemistry; and the pharmaceutical industry.[325] Appointments are made by the Health and Agriculture Ministers "after consultation with such organisations as they consider appropriate"[326] and are for a period of four years.[327] The Ministers appoint one of the members of the Commission to be the chairman.[328] There are currently 19 members of the Commission and the present chairman is Professor D.H. Lawson. Appendix XIV contains a list of the current members of the Commission.

The Medicines Commission does not have any standing sub-committees, although it has, in the past, appointed *ad hoc* committees to investigate and prepare reports on

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[324]Medicines Commission (1971).
[325]Section 2(2) and 2(3).
[326]Section 2(2).
[327]The Medicines Commission and Committees Regulations 1970 (S.I.No. 746).
[328]Section 2(4).

issues of concern such as, prescription only medicines, general sale lists,[329] child safety,[330] oral contraceptives,[331] the quality control of sterile products,[332] and liability for defective products.[333]

Section 3(2) of the Act lists the specific duties of the Commission and these are included in the Commission's terms of reference:

" a. making recommendations to the Ministers with regard to the number of Committees to be set up under Section 4 of the Act, and the functions to be assigned to each such committee;

b. recommending to Ministers persons well qualified to serve as members of a committee set up under Section 4 of the Act;

c. reviewing these committees from time to time and recommending any changes considered appropriate in their number and functions;

d. undertaking functions of the kind normally assigned to one of these committees if at the time no appropriate committee exists." [334]

Also included in the terms of reference are the following additional statutory duties:

" In accordance with Part II of the Act, the Commission consider representations made (either in writing or at a hearing) by an applicant or licence holder where the licensing authority has been advised by a committee set up under Section 4 of the Act to refuse, suspend or revoke or vary a licence or certificate, and report its findings and advice, and the reason for its advice, to the licensing authority."[335]

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[329]Medicines Commission (1971).
[330]Medicines Commission et al (1974).
[331]Medicines Commission et al (1977).
[332]Medicines Commission et al (1973).
[333]Medicines Commission et al (1979).
[334]Medicines Commission et al (1995) p8.
[335]Ibid.

and

> " Sections 99 - 102 of the Act confer on the Commission functions in relation to publication of the British Pharmacopoeia, other compendia, lists of names and other relevant works." [336]

Section 5(5) gives Ministers the power to confer a new function on the Commission or to terminate or vary an existing function.[337] The Ministers can also add to, revoke or vary any of the provisions of Schedule 1 which refer to the Commission.

The Medicines Commission is required by the Act to produce annual reports.[338] These annual reports provide a useful, although not detailed, outline of the work carried out by the Commission. An analysis of these reports revealed that the main regular areas of work for the Commission have been: the implementation of the Medicines Act 1968; the implementation of European Directives relating to medicinal products; the appointment of section four committee members; the supervision of the work of these committees; licensing appeals (see Table 20); consultation regarding the introduction or amendment of statutory instruments; the appointment of working parties or *ad hoc* committees to study particular problems; the recommendation for publication of the British Pharmacopoeia and British Approved Names; analysis and provision of advice relating to the work of the Committee on Proprietary Medicinal Products and the Pharmaceutical Committee; and analysis of any relevant publications, proceedings at conferences and developments in other countries.

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[336]Ibid.
[337]This is subject to Parliamentary approval.
[338]Section 5(2) requires the Medicines Commission to submit an annual report to Ministers.

Table 20 Licensing Appeals relating to Medicinal Products for Human Use dealt with by the Medicines Commission (1973 - 1996).[339]

1973	1 written representation	**1985**	5 hearings; 7 written representations
1974	3 hearings/written representations (not specified fully)	**1986**	7 hearings; 8 written representations
1975	3 hearings	**1987**	12 hearings; 12 written representations
1976	3 hearings	**1988**	13 hearings; 6 written representations
1977	5 hearings	**1989**	6 hearings; 6 written representations
1978	1 hearing	**1990**	8 hearings; 1 written representation
1979	2 hearings; unspecified number of written representations	**1991**	9 hearings; 4 written representations
1980	5 hearings; 6 written representations	**1992**	9 hearings; 4 written representations
1981	5 hearings; 4 written representations	**1993**	1 hearing
1982	10 hearings	**1994**	5 hearings
1983	13 hearings; 2 written representations	**1995**	10 hearings; 2 written representations
1984	8 hearings; 1 written representation	**1996**	3 hearings

Further analysis of the annual reports revealed some of the important matters considered by the Commission from 1969 until present as including: the legal status of medicinal products; child safety; product liability; homeopathic medicinal products; the free movement of medicinal products within the European Community; and the regulation of medical devices. A full list of these matters is contained in Appendix XV. The work of the Medicines Commission will be discussed further in Chapter Four, in relation to alleged conflicts of interest.[340]

C. The Committee on Safety of Medicines (CSM)

The CSM was established in 1970 to give advice with respect to the safety, quality and efficacy of medicinal products for human use and to promote the collection and investigation of information relating to adverse reactions.[341]

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[339]The figures for this table were extracted from the annual reports of the Medicines Commission. Some of the hearings or written representations dealt with more than one product at a time. The Commission also dealt with appeals relating to medicinal products for veterinary use.

[340]p204.

[341]SI 1970/1257. See Chapter Two for information on the documents issued by the CSM.

The CSM also advises on European licence applications.[342] Professor Asscher, Chairman of the CSM from 1987 to 1992, gave a useful insight into the work of the CSM in relation to licence applications:

> " The Committee's work is 'pre-digested' by a number of sub-committees [...] The professional staff of the Medicines Control Agency (MCA) [...] prepares summaries and the sub-committees discuss draft advice which is to be presented by their chairmen at the monthly meetings of the main Committee; each meeting lasts one to two days. All members of the sub and main Committees are allowed access to all of the companies' submissions, but usually it is only the member(s) with expert knowledge of the subject that is expected to study all of the original data. More than 90% of the workload of the MCA is undertaken by its own professional staff without reference to the committees. The MCA staff refers to the Committees in the case of product licence or clinical trial certificate applications for new products or in any instance where they are in doubt and feel in need of advice. They are also by law required to refer proposals to refuse to renew or to suspend or revoke licences on grounds related to safety, quality or efficacy. It is not commonly appreciated that the professional staff of the MCA can and often does give advice to the Licensing Authority to approve licence applications. What they cannot do is to advise refusal without reference to the section four Committees. On occasions, therefore, the CSM is blamed for advice it never gave or delays it did not cause. What is more, CSM's advice may be overruled by the Licensing Authority, sometimes on the advice of the Medicines Commission, yet the media invariably attribute all decisions concerning the licensing of medicines to the CSM." [343]

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[342]Medicines Commission et al (1995) p13.
[343]Asscher (1990).

Table 21 sets out the numbers of product licence (PL)/marketing authorisation (MA) applications (discussed later in this Chapter[344]), clinical trial certificate applications, appeals and adverse reactions, which the CSM has dealt with since 1970.

Table 21 Analysis of the Work of the CSM (1970-1996)[345]

Year	PL/MA Applications	Clinical Trial Certificate Applications	Appeals	Adverse Reactions
1970	-	-	-	3,601
1971	89	50	6	2,837
1972	406	153	48	3,638
1973	359	172	20	3,619
1974	418	131	27	4,818
1975	328	104	11	5,052
1976	506	127	21	6,490
1977	286	64	55	11,255

[344]p134.
[345]Statistics have been taken from the CSM's annual reports.

Table 21 contd.

Year	PL/MA Applications	Clinical Trial Certificate Applications	Appeals	Adverse Reactions
1978	191	45	42	11,873
1979	180	62	48	10,840
1980	167	46	78	10,179
1981	159	36	66	13,032
1982	191	7	44	10,922
1983	*169*	*11*	*61*	*12,689*
1984	103	15	53	12,163
1985	119	8	40	12,652
1986	77	10	36	15,527
1987	120	7	32	16,431
1988	163	8	40	19,022
1989	200	0	52	19,246
1990	232	0	40	18,084
1991	300	0	43	20,272
1992	242	1	33	21,498
1993	196	0	44	19,686
1994	151	0	39	17,700
1995	150		34	17,668
1996	156	-	43	17,191

In addition to dealing with licence applications and adverse reactions to medicinal products, the CSM also regularly comments on "matters of medical and

pharmaceutical relevance".[346] These have included bovine spongiform encephalopathy, carcinogenicity studies, advertising, delays in licensing, ethical aspects of clinical trials, European regulations and drug use in the elderly. Appendix XVI lists all of these matters as discussed in the CSM's Annual Reports from 1971 to 1997.

The CSM has recently reviewed its working arrangements "in the light of the new European systems and procedures which it now has to operate."[347] On 11 December 1995 the Minister for Health, Gerald Malone, announced:

> " The Committee has concluded that, in order to meet its obligations, it must meet fortnightly rather than monthly, and must have more members in order to operate under a more flexible timetable, The Committee has also taken the opportunity to increase the number of additional expert advisers it can consult, and who can be asked to attend meetings when required." [348]

The number of members of the CSM has increased from 21 members in 1995 to 30 members in 1996/97. The current members are listed in Appendix XIV. A list of the 66 expert advisers who have agreed to assist both the CSM and the MCA is also contained in Appendix XIV.

Over the years, the CSM has appointed various sub-committees to assist it in its work: the Safety, Efficacy and Adverse Reactions Sub-Committee(SEAR);[349] the Adverse Reaction Group of SEAR (ARGOS);[350] the Standards of Herbal Products Sub-Committee;[351] the Joint Sub-Committee on Antimicrobial Substances;[352] the Sub-Committee on Toxicity, Clinical Trials and Therapeutic Efficacy; the Sub-

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[346]Medicines Commission et al (1995) p18.
[347]MCA (1996a) p7.
[348]Ibid.
[349]Medicines Commission et al (1983).
[350]Ibid.
[351]Medicines Commission et al (1975) p17.
[352]Medicines Commission et al (1974) p20.

Committee on Adverse Reactions,[353] the Joint Sub-Committee on Adverse Reactions to Vaccines and Immunological Products (ARVI); [354] and the Sub-Committee on Safety and Efficacy.[355] All of these sub-committees have been abolished and there are three sub-committees in current operation: the Sub-Committee on Biological Substances (BIOLS), which was set up in 1971 to examine vaccines and immunological products;[356] the Sub-Committee on Chemistry , Pharmacy and Standards (CPS), which was established in 1971 to examine the "proposed method of manufacture, specification and quality control of new products";[357] and the Sub-Committee on Pharmacovigilance (SCOP), which was established in 1992 to "advise the Committee on the safety of marketed medicines, and to develop strategies on postmarketing surveillance".[358]The current membership of these sub-committees is also listed in Appendix XIV.

At various times, the CSM has appointed its own Working Parties or joined with other organisations to examine issues such as: oral contraceptives;[359] the carcinogenicity testing of therapeutic substances;[360] LD50;[361] beta adrenoceptor blocking agents;[362] pertussis vaccine;[363] data requirements for Clinical Trial Certificate applications;[364] adverse reactions and postmarketing surveillance;[365] the implications of Bovine Spongiform Encephalopathy (BSE) for human medicinal products;[366] and beta-agonists.[367]

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[353]CSM (1972a).
[354]Medicines Commission et al (1980) p6.
[355]Medicines Commission et al (1993) p13.
[356]CSM (1972a) p.6.
[357]Ibid.
[358]Medicines Commission et al (1993) p13
[359]Medicines Commission et al (1976)
[360]Medicines Commission et al (1977).
[361]Medicines Commission et al (1978).
[362]Medicines Commission et al (1977).
[363]Medicines Commission et al (1979)
[364]Ibid.
[365]Medicines Commission et al (1985) and (1988).
[366]Medicines Commission et al (1990).
[367]Medicines Commission et al(1992).

The work of the CSM will be discussed further in Chapter Four with reference to alleged conflicts of interest and pharmacovigilance.[368]

D. The British Pharmacopoeia Commission

The British Pharmacopoeia Commission was established in 1970 for the following purposes:

" (a) the preparation under section 99(1) of the Act of any new edition of the British Pharmacopoeia;

(b) the preparation under section 99 (1) of the Act , as given effect by section 102(1) thereof, of any amendments of the edition of the British Pharmacopoeia published in 1968 or any new edition of it; and

(c) the preparation under section 100 of the Act (which provides for the preparation and publication of lists of names to be used as headings to monographs in the British Pharmacopocia) of any list of names and the preparation under that section as given effect by section 102(2) of the Act of any amendment of any published list." [369]

The Commission also provides advice to the United Kingdom delegation to the European Pharmacopoeia Commission (of which the UK is a member by virtue of its obligations under the Convention on the Elaboration of a European Pharmacopoeia Treaty Series No 32: 1974).[370]

An MCA publication explained the value of the work of the Pharmacopoeia Commission, as follows:

" The Pharmacopoeia is an important statutory component of the overall system of the control of medicines and complements the licensing and inspection processes of the MCA. Pharmacopoeial standards are published and readily available to all

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[368]p204 and p262.
[369]SI 1970/1256.

> who need to use them - suppliers, purchasers, medicines regulators or independent laboratories. They provide the manufacturing industry with a clear yardstick of quality for many commonly used medicines and their ingredients. Pharmacopoeial standards contribute to an assurance of identity and purity of these medicines and their constituents throughout their shelf-life."[371]

The current membership of the Pharmacopoeia Commission is listed in Appendix XIV. Since 1970, the Commission has appointed various advisory Committees and Consultative Groups. At present, there are twelve Committees: Medicinal Chemicals (three groups); General Chemicals; Antibiotics; Pharmacy; Crude Drugs and Galenicals; Biological Materials; Immunological Products; Surgical Dressings; and Nomenclature.[372] There are also three Consultative Groups: Human and Veterinary Medicines; Radioactive Materials; and Plastics and Plastic Containers.[373]

The most recent publications prepared by the Pharmacopoeia Commission have included: the British Pharmacopoeia 1993, which contains 2040 monographs for substances and articles used in the practice of medicine, surgery, dentistry, midwifery and veterinary medicine; the 1995, 1996 and the 1997 Addenda to the British Pharmacopoeia 1993; Amendments Nos.1, 2, 3, 4 and 5 to the British Pharmacopoeia 1993; the British Pharmacopoeia (Veterinary) 1993, a companion volume to the British Pharmacopoeia 1993, which contains standards for substances, preparations and immunological products used solely in veterinary medicine; the 1995 Addenda to the British Pharmacopoeia (Veterinary) 1993; Amendments Nos. 1, 2 and 3 to the British Pharmacopoeia (Veterinary) 1993, Supplement Nos. 1, 2 and 3 to British Approved Names 1994. A CD-ROM version of these texts has also been

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[370]Medicines Commission et al (1995) p47.
[371]MCA (1993g) p23.
[372]Medicines Commission et al (1997) pp65-66.
[373]Ibid p66.

published.[374] Appendix XVII sets out an example of the monograph for aspirin, published in the British Pharmacopoeia 1993.

Another important part of the work of the Pharmacopoeia Commission is its liaison with a number of organisations including: the National Institute for Biological Standards and Control; the Veterinary Medicines Directorate; the United States Pharmacopoeia; the United States Adopted Names Council; the Australian Therapeutic Goods Administration Laboratories; the Canadian Health Protection Branch; Health and Welfare; several official laboratories in countries, which are party to the Convention on the Elaboration of the European Pharmacopoeia; and the Pharmaceuticals Unit of the World Health Organisation.[375]

E. The Committee on Dental and Surgical Materials (CDSM)

The CDSM was established in 1975[376] and disestablished on 1 January 1995 because responsibility for the products for which the CDSM was concerned, was transferred to the Medical Devices Agency following the implementation of various European Directives relating to medical devices.[377] Its terms of reference were:

> "a. to give advice with regard to the safety, quality and efficacy in relation to human or animal use of:
>
> (i) substances or articles for dental or surgical use being instruments, apparatuses or appliances to which any provision of the Medicines Act 1968 is applicable or medicinal products or other substances or articles (not being instruments, apparatuses or appliances) to which any provision of the Medicines Act 1968 is applicable and in respect of which neither the Committee on Safety of Medicines nor the Veterinary Products Committee

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[374]Medicines Commission et al (1994) and (1995).
[375]Ibid.
[376]SI 1975/1473.
[377]S.I. 1994/3120. Medical devices are discussed further in Chapter Four.

is the appropriate Committee, whether or not used in conjunction with any other such substance, article, instrument, apparatus or appliance.

(ii) substances and fluids described in paragraph 2 of Schedule 1 to the Medicines (Specified Articles and Substances) Order 1976 (substances and fluids for use with contact lenses or blanks).

b. to promote the collection and investigation of information relating to adverse reactions for the purpose of giving such advice." [378]

The CDSM gave advice to the Licensing Authority on product licence applications, renewals, variations, appeals and adverse reactions concerning the following therapeutic classes of product :

" i. surgical materials such as bone cements, tissue adhesives etc.;

ii. certain dressings etc. in which the medicine is intended to have a curative function and is not limited to sterilising the dressing;

iii. intra-uterine contraceptive devices and any other instrument, apparatus or appliance inserted in the uterus (including the cervix) for the purpose of contraception;

iv certain vaginal and tubal contraceptives;

v. other surgical materials in the form of:

a. ligatures, sutures, binding materials etc. prepared from the tissue of an animal and used wholly or partly in surgical operations;

b. any other surgical ligature or suture etc. prepared from any source which is capable of being absorbed by the body tissues;

c. any absorbent or protective material capable of being absorbed by the body and used wholly or partly for use in surgical operations;

vi. contact lens fluids;

vii. certain medicines placed in the eye;

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[378]Medicines Commission et al (1994) p31.

vii. **all licensable dental materials and medicines used specifically for the treatment and prevention of dental disease, including local anaesthetics used in dental practice."** [379]

One sub-committee and three working parties assisted the CDSM in its work: the Sub-Committee on Ophthalmic Products[380] the Sutures Working Party;[381] Working Group on the Draft European Medical Devices Directive;[382].and the Contact Lens Solutions Working Group.[383]

Table 22 lists the product licence and clinical trial certificate applications dealt with by the Committee.

Table 22 Product Licence and Clinical Trial Certificate Applications dealt with by the CDSM (1977 - 1994)[384]

Year	PL applications	CTC applications	Year	PL applications	CTC applications
1977	6	4	1986	36	0
1978	12	3	1987	61	0
1979	22	3	1988	42	0
1980	21	2	1989	62	0
1981	112	1	1990	51	0
1982	79	1	1991	38	
1983	141	0	1992	21	0
1984	100	2	1993	28	0
1985	79	4	1994	13	8

In its final annual report, the CDSM discussed its work from 1975 to 1994. In particular, the CDSM said that it had been concerned with two categories of product: intrauterine contraceptive devices and contact lens solutions.

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[379]Medicines Commission et al (1995).
[380]Medicines Commission et al (1977).
[381]Medicines Commission et al (1993).
[382]Ibid
[383]Medicines Commission et al (1994).
[384]Statistics taken from annual reports of the CDSM. See Medicines Commission et al (1976) to (1995).

" The importance of the Committee's role was illustrated by the discovery that about half of the contact lens products on the market at that time were unable to meet acceptable standards of safety, quality and efficacy. Firm action was taken whenever benefit to risk was unacceptable and the principle was established that these products, used daily by thousands of people, should attain high standards. Public safety was the essence of the CDSM's work." [385]

The CDSM felt that one of its most important achievements had been:

" the constructive work it did to help pave the way for the Medical Devices Directive 93/42/EEC especially by:

- calling attention to the need for legislation on medical devices, for example, following reports of catastrophic failure of heart valves,
- providing input to draft Directives as they were negotiated in Brussels, and
- bringing together expert comment through, for example, the working party on contact lens solutions, which helped the move towards the new EC system." [386]

Although the CDSM has been abolished, many of its members have offered to "give their expertise in the future arrangements".[387]

F. The Committee on the Review of Medicines (CRM)

The CRM was established in 1975[388] and its terms of reference were:

" To consider and give advice on the safety, quality and efficacy, in relation to human use, of any substance or article to which any provision of the Medicines

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[385]Medicines Commission et al (1995) p40. In relation to adverse reactions, the CDSM was responsible for:
" • setting up the Yellow Card Scheme for Optometrists
• the timely and prescient action taken in 1987 in warning surgeons of the dangers of CJD (Creutzfeldt-Jacob Disease) in relation to human dural implants, and
• warning of wound dehiscence after damage to certain synthetic sutures, followed up by formulating guidelines for assessing the performance of such materials." Ibid.

[386]Ibid.

[387]Ibid.

Act is applicable in connection with the review by the Licensing Authority of the safety, quality and efficacy of substances or articles in respect of which product licences granted under Part II of the Act are in force.

The CRM is concerned mainly with medicines which already were on the market when the Medicines Act came into force and which have Product Licences of Right (PLRs). Unless subject to one of the exemptions to the EEC pharmaceutical directives, all products with PLRs must be reviewed so as to ensure that they meet the standards imposed by those directives (of which the principal ones relevant to such products are 65/65/EEC, 75/318/EEC and 75/319/EEC)." [389]

The review of these products had to be completed by 20 May 1990.[390] These terms of reference are interesting in that they include the first reference to licensing work having to be carried out in accordance with European Directives. These Directives will be discussed later in this Chapter.

It was mentioned earlier that the Committee on Safety of Drugs was not responsible for medicinal products introduced prior to 1964, and it emphasised the need for review:

" Medicines are not sacrosanct however, simply because they have been in use for a long time. To give but one example, bromides have been widely used for years. It should not, however, be thought that they are innocuous. Chronic intoxication with them is an insidious, not uncommon and potentially serious condition. The Committee believes that medicines containing bromides should be taken only under medical supervision. The Committee notes that under forthcoming legislation provision is to be made for retrospective review."[391]

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[388]SI 1970/1006.
[389]Medicines Commission et al (1991) p30.
[390]Winship et al (1992).
[391]CSD (1968) p10.

In the White Paper, "Forthcoming Legislation on the Safety, Quality and Description of Drugs and Medicines", it was envisaged that:

> " It will not be practicable to license all existing drugs before the licensing system for new drugs and formulations starts. There will therefore be temporary provisions to enable products effectively on the market before the appointed day for the beginning of licensing of new drugs to continue without a licence until they can be brought under the licensing scheme later."[392]

On 1 September 1971, the "first appointed day" for the commencement of licensing, the Licensing Authority issued 39,035 Product Licences of Right (PLR).[393] However, 6,000 PLRs relating to homeopathic products, blood products, vaccines, toxins, sera and radiopharmaceuticals were excluded from the review by Article 34 of Directive 75/319/EEC.[394]

> " The remaining PLRs had to be reviewed and either full product licences granted or the PLRs allowed to lapse and the products taken off the market." [395]

Sections 25 to 27 of the Medicines Act set out various provisions relating to Product Licences of Right; Medicines Division issued "Notes on the Preparation of Summaries of Information for Products Subject to the Review Procedure".[396]

The CRM was assisted in its work by the CDSM and sub-committees on anti-rheumatic agents, analgesics, psychotropic agents and immunological products.[397] In 1983, the CRM commented:

> " Last year's report expressed the Committee's concern on a number of apparently hazardous and inefficacious products under examination. It continues to be a matter for surprise and concern that the examination of the safety, quality and

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[392]p7.
[393]Medicines Commission et al (1992).
[394]Ibid. According to Winship et al (1992), these remaining products will be reviewed eventually. See also the discussion of "relevant medicinal product" later in this chapter.
[395]Medicines Commission et al (1992) p41.
[396]Medicines Division (1987).

> efficacy for the first time of products which have been marketed for a number of years should discover that substances of well-known toxicity are included in such products. The Committee will, of course, continue to pursue with vigour cases of this type which are referred to it."[398]

In its final annual report, the CRM outlined its work: the review was split into 3 stages and of the 34,139 PLRs eligible for review, approximately 6,300 licence applications were received, and of these, approximately 5,300 reviewed licences were granted.[399] The CRM suggested possible reasons why so many products did not continue through the review process:

> " Many products were withdrawn voluntarily because they were outdated or because their sales were too small to warrant pursuit of a reviewed product licence. Other products were withdrawn once the licence holders found they could not answer pertinent questions from the CRM."[400]

Winship et al listed some of the policy reviews issued by the CRM[401] and Table 23 lists some of the medicinal products which were reviewed by the CRM.

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[397]Medicines Commission et al (1976).
[398]Medicines Commission (1984) p45.
[399]Ibid p42.
[400]CRM (1986).
[401] "Standardisation of pregnancy warnings on data sheets (Curzen); Herbal products for self-limiting conditions; Bismuth salts; Camphor: indications and concentrations; Cold cure remedies; Comfrey: hazards; Corticosteroids: oral, injectable and topical; Cytotoxics: handling and reconstitution; Digoxin and bioavailability; Diuretics; Nitrofurantoin; Phenytoin and bioavailability; Preservation of antacid suspensions; Sucrose in paediatric medications; Sulphonamides; Tetracyclines; Unopposed oestrogens: toxicity; and Vasodilators." [(1992) p586]. See also CRM (1977), (1978), (1979) and (1980).

Table 23 Medicinal products reviewed by the CRM (1975 - 1991)[402]

Achillae, Alclofenac, Allopurinol, Aloxiprin, Aminophylline, Amitriptyline, Amphetamines, Anti-human lymphocyte globulin (horse), Ascophyllum Nodusum, Aspirin, Azathioprine, Barbiturates, BCG vaccine, Benorylate, Benzoctamine, Black cohosh, Blue cohosh, Bromide salts, Butriptyline, Caffeine, Calcium hydroxide, Cantharidin, Carisoprodol, Celery, Chloral hydrate, Chlordiazepoxide, Chlormezanone, Chloroquine, Cholera vaccine, Chymotrypsin, Clobazam, Clofibrate, Clomipramine, Clorazepate, Codeine, Colchicine, Comfrey, Corticosteroids, Crude liver extracts, Cyclophosphamide, Cytotoxics, Desipramine, Dextromoramide, Dextropropoxyphene, Diamorphine, Diazepam, Dibenzepin, Dichloral Phenazone, Diethylpropion, Digoxin, Dihydrocodeine, Diphtheria antitoxin immunosera, Diphtheria/Tetanus/Pertussis vaccine, Dothiepin, Dover's powders, Doxepin, Ephedrine, Ethoheptazinecitrate, Ethosalamide, Ethylmorphine, Fenfluramine, Fenoprofen, Feprazone, Ferrous Fumarate, Flufenamic acid, Flupenthixol, Flurazepam, Garlic, Glutethimide, Gripe water preparations, Griseofulvin, Hexachlorophane, Hydroxychloroquine, Ibuprofen, Imipramine, Indomethacin, Influenza vaccine, Iprindole, Ketoprofen, L-tryptophan, Laminaria, Levorphanol, Liquid paraffin, Lithium, Lorazepam, Magnesium salts, Maprotiline, Mazindol, Measles vaccine, Medazepam, Mefanamic acid, Meprobamate, Methadone, Methaqualone, Methocarbamol, Methotrimeprazine, Methyl Salicylate, Methylprylone, Mianserin, Mineral salts, Monoamine oxidase inhibitors, Morazone, Morphine, Morphine, Mumps vaccine, Naproxen, Neomycin, Nifenazone, Nitrazepam, Nitrofurantoin, Nomifensine, Non-parenteral bacterial vaccines, Nortriptyline, Opipramol, Opium, Oxazepam, Oxycodone, Oxyphenbutazone, Pantothenic acid, Papaveretum, Paracetamol, Penicillamine, Pennyroyal, Pentazocine, Pethidine, Phenacetin, Phenazocine, Phenazone, Phenelzine, Phenmetrazine, Phentazocine, Phentermine, Phenylbutazone, Phenylsemicarbazide, Phenytoin, Piritramide, Podophyllum, Poliomyelitis vaccine, Potassium aminobenzoate, Potassium nitrate, Potassium p-aminobenzoate, Potassium salts, Prickly ash, Probenecid, Protriptyline, Rabies vaccine, Rubella vaccine, Salicylamide, Sassafras, Schick test toxin, Smallpox vaccine, Snake venom antisera, Sodium Aurothiomalate, Sodium Salicylate, Sodium salts, Sulphinpyrazone, Sulphonamides, Sulphur (oral), Sulphur-guaiacum preparations, Tartrazine, Temazepam, Tetanus antitoxin, Tetanus vaccine, Thyroid extract, Tranylcypromine, Triazolam, Triclofos sodium, Trimipramine, Turpentine oil, Typhoid vaccine, Uva ursi (bearberry), Valerian, Vasodilators, Viloxazine, Vitamins, and Yellow fever vaccine.

Having completed the review of medicinal products, the CRM was disestablished in 1992.[403]

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[402]Based on the annual reports issued by the CRM. See Medicines Commission et al.
[403]SI 1992/606.

3.6 Developments since 1995: The New Licensing System

3.6.1 Proposals for European Harmonisation[404]

In 1965, the European Commission issued the first Directive relating to medicinal products, "Council Directive of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products".[405] It could be argued that this was the EC's response to thalidomide and Cartwright has commented that, following the withdrawal of thalidomide there was:

> " clearly a need for legislation to regulate the marketing of pharmaceutical products and to supersede national controls with a more comprehensive EC system." [406]

The preamble to this first Directive sets out the objectives of the EC in relation to medicinal products:

> " The primary purpose of any rules concerning the production and distribution of medicinal products must be to safeguard public health. [...] However, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community. [...] Trade in medicinal products within the Community is hindered by disparities between certain national provisions, in particular between provisions relating to medicinal products (excluding substances or combinations of substances which are foods, animal feeding stuffs or toilet preparations) and [...] such disparities, directly affect the establishment and functioning of the common market. [...] Such hindrances must accordingly be removed and [...] this entails approximation of the relevant provisions. [...] However, such approximation can only be

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[404] See Weatherall and Beaumont (1995) for a history of the development of the European Community.
[405] 65/65/EEC. The title was amended by Directive 89/341/EEC: "proprietary medicinal products" has been changed to "medicinal products".

> achieved progressively and [...] priority must be given to eliminating the disparities liable to have the greatest effect on the functioning of the common market." [407]

This Directive consists of five chapters: "Definitions and Scope"; "Authorization to place proprietary medicinal products on the market"; "Suspension and revocation of authorizations to market proprietary medicinal products"; "Labelling of proprietary medicinal products"; and "General and Final Provisions".

More Directives relating to medicinal products did not appear until ten years after the first Directive. Hancher explained that negotiations on other earlier draft Directives were stalled for two reasons:

> " First, it was difficult to obtain a consensus on the question of the qualifications of the 'experts' who were to be responsible for evaluating submissions for marketing authorizations. The considerable divergence between the Member States on the status of, as well as the requirements for entry into, the pharmaceutical profession proved a particular obstacle here, especially as general progress on the harmonisation of the rules of establishment relating to this profession was slow. Secondly, the West German government, never a keen supporter of stricter marketing regulation, refused to abandon its own system of simple product registration, unless the other Member States agreed to introduce mutual recognition procedures at the same time, thus opening up their markets to the commercially powerful German firms." [408]

Hancher further commented that the harmonisation of legislation relating to medicinal products was made more difficult by the "peculiarities of the pharmaceutical market":

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[406]Cartwright and Matthews (1991) p34.
[407]65/65/EEC.
[408]Hancher (1992) p13.

" In summary, the pharmaceutical market is one which is closely regulated at national level, and it is a market to which the ordinary rules of competition cannot easily be applied. The successful completion of a single unified market however, requires not only the harmonisation of these divergent national rules, but also the elimination of potential anti-competitive practices on the part of undertakings which tend to compartmentalise the Common Market and which prevent the emergence of both intra- and inter-brand competition." [409]

In 1975, two Directives were issued: Directive 75/319/EEC, known as the "Second Directive" and Directive 75/318/EEC, known as the "Norms and Protocols Directive". Both these Directives and Directive 65/65/EEC formed the basis of the European regulation of medicinal products.

The Commission continued to issue Directives and, in 1985, it published a White Paper, which proposed a timetable of specific measures to complete all aspects of the "Internal Market" by 1992. In relation to medicinal products, the Commission set out the following requirements:

" • Proposals for Directive concerning the placing on the market of high technology medicinal products including those derived from biotechnology.
- Proposal amending Directive 75/318/EEC concerning the testing of medical specialities.
- Proposal amending Directive 81/852/EEC concerning veterinary medicinal products.
- Proposal for a Council Recommendation concerning tests relating to the placing on the market of medical specialities.
- Proposal for a Council Directive amending Directive 65/65/EEC concerning medical specialities.
- Price transparency in prices of medicines and social security refunds.

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[409] Ibid pp10-11.

- Membership of the European Pharmacopocia.
- Extension of Directives to medicinal products not already included.
- Amendment to the Directive on veterinary medicines.
- Pharmaceutical products - completion of work eliminating obstacles to free circulation of pharmaceutical products.
- Harmonisation of condition of distribution to patients.
- Information of (sic) doctors and patients."[410]

In 1989, the Commission produced an update on the progress of the "white paper programme",[411] and by 1993, all the proposals had been implemented.

Articles 30 to 36 of the EC Treaty set out provisions with regard to the free movement of goods. Article 36 states that Member States can restrict or prohibit the free movement of goods on the grounds of the "protection of health and life of humans". According to the Commission, there have been five important consequences for the free movement of medicinal products within the European Community, which have resulted from the harmonisation of legislation:

" • The sole [sic] criteria which may be taken into consideration by the Member States during the examination of an application for authorization are the quality, safety and efficacy of the product concerned. These criteria have been progressively harmonised, as have certain aspects of the procedures for granting marketing authorizations (time limits, giving of reasons, publication of decisions etc.).
- Analytical, pharmaco-toxicological tests and clinical trials which have been conducted in accordance with the Community rules need no longer be repeated within the Community.
- The batch control reports of the manufacturer are accepted by the other Member States without repetition of the individual control tests.

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[410]Commission (1985), Annex pp17-18.
[411]Commission (1989) p22.

- **The general requirements regarding labelling and package inserts have been harmonised.**
- **A common list of colouring matters approved for use throughout the Community has been adopted."** [412]

In Chapter Two, the Author discussed the means by which European legislation and materials relating to medicinal products were obtained.[413] The Author also discussed that there are different types of European legislation.[414] Directives are the most often used type of legislation for the introduction of new European legislative provisions relating to medicinal products. Directives are binding on Member States with regard to their objectives but allow the Member States to implement the provisions of the Directives into their national law by the most suitable means.[415] In the UK, directives are often implemented by way of statutory instruments. Appendix IV lists every European Directive and Regulation together with every Decision, Recommendation, Opinion and Proposal relating to medicinal products and medical devices.[416] Appendix IV also lists the statutory instruments, which have implemented provisions of these Directives and Regulations into UK legislation.

3.6.2 The Medicines for Human Use (Marketing Authorizations Etc.) Regulations 1994: Introduction and Effect on the Medicines Act 1968

It was not until 1995, that the "Future Systems" package of legislation, part of the earlier White Paper proposals and "designed to complete the EC single market in pharmaceuticals",[417] was implemented into UK law by The Medicines for Human

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[412]Commission (1991) p4.
[413]p30.
[414]Ibid.
[415] See Appelbe and Wingfield (1997) p371 for a discussion of the European Community and the effects on medicinal products and pharmacists.
[416] The various forms of European Legislation and proposals are explained in Chapter Two.
[417]Regulation 2309/93, Directive 93/39/EEC amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC, and Directive 93/41/EEC, repealing Directive 87/22/EEC. See MCA (1994g)

Use (Marketing Authorizations Etc.) Regulations 1994 (the "1994 Regulations").[418]

From 1 January 1995, two new licensing procedures were established:

> " • The "centralised procedure", mandatory for certain high technology products and optional for others, leading to the grant of an EC marketing authorization valid in all Member States, with variations, renewals and any post-licensing action necessary on public health grounds also determined at Community level.
>
> • The "decentralised procedure", based on the recognition of a national marketing authorization granted by one Member State by other Member States on application by the company, with binding EC arbitration in the event of differences between the Member States concerned, and with arrangements for harmonising subsequent variations, renewals and any post-licensing action."[419]

It is proposed, by the Author, that the implementation of the "Future Systems" package of legislation is the most important development in the history of the regulation of medicinal products in Europe and the UK since the implementation of the Medicines Act 1968. In effect, the 1994 Regulations have replaced the 1968 Act as the legal basis for licensing the majority of medicinal products.[420] The 1994 regulations also affected product licences granted under the Medicines Act before 1 January 1995. These licences are now treated as "UK Marketing Authorizations" in terms of the new regulations.[421]

These legislative changes have also led to the replacement of the "Multi-State" and "Concertation" European licensing procedures, by the decentralised and centralised procedures.[422] The original version of the Multi-State procedure was introduced by

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[418]S.I. No. 3144.
[419]Ibid. The MCA have published information concerning the operation of the decentralised and centralised procedures in "Future Systems. A Guide to New Arrangements for the Licensing of Medicinal Products for Human Use in the European Community." See MCA (1993k).
[420]MCA (1995a) p14. The exceptions are discussed in the next section.
[421]Schedule 6.
[422]See Cartwright (1992) and Charlesworth (1988) for further details.

Directive 75/319 and was operational in 1978. This procedure was "hardly used by the pharmaceutical industry"[423] and one commentator went so far as to say that the Multistate Procedure had been:

> " a total failure and the reluctance of Member States and pharmaceutical companies to make the system work does not bode well for the success of the European single market." [424]

This licensing procedure was amended by Directive 83/570 and the new procedure came into operation in 1986. In 1987, Directive 87/22 introduced a licensing procedure for high technology medicinal products: the "concertation" procedure. Charlesworth commented:

> " The multistate and concertation procedures have provided a basis on which Member States can examine the compatibility of their different approaches to medicines regulation. Experience with the multistate procedure suggests that mutual recognition has not been very effective. The concertation procedure, which is in principle based on a single assessment made by Member States in collaboration with each other, has worked more effectively but has not prevented Member States from making their own final decisions on whether and how to authorise a product within their own national boundary." [425]

The legislative changes contained in the 1994 Regulations have also led to the establishment of the European Agency for the Evaluation of Medicinal Products (EMEA).

> " The Europe of medicinal products is entering a new phase. The opening of the European Agency for the Evaluation of Medicinal Products represents the fruition of efforts undertaken since the 1970s to harmonise pharmaceutical legislation. It

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[423] Quoted from COM(88)143. The work of the CPMP and these earlier licensing procedures is detailed in various "Reports from the Commission on the activities of the CPMP" - COM(81)363, COM(82)787, COM(88)143 and COM(91)39. Also, information can be found in Poggiolini and Donawa (1990), EFPIA (1988a), Charlesworth and Griffin (1988) and Cartwright and Matthews (1991).
[424] Donnelly quoted in SCRIP (1991e).
[425] Griffin, ed. (1992) p74.

shows the will of the European Union to focus as much as possible on the concerns of European citizens: health, and quality and safety of health care." [426]

The MCA explained how the European provisions were implemented into UK legislation:

" The Regulations bring the new procedures into UK law mainly through cross-reference to the relevant Community provisions, rather than by setting them out in full, as has generally been done in the past. This new approach has the advantages of avoiding duplication between UK and EC law, ensuring that EC law is implemented in full, and ensuring that UK law is updated with minimum complication when changes are made to EC legislation."[427]

It was further stated that this would

" provide a much clearer and more coherent statement of the relevant law than would have been achieved by further amendments of the Medicines Act, which has already been substantially amended in recent years." [428]

The "relevant Community provisions" include:

" Council Directive 65/65/EEC; 75/318/EEC; Chapters I to II and V to VI of Council Directive 75/319/EEC and any regulation adopted by the Commission under Article 15 of that Directive; Council Directive 89/342/EEC; Council Directive 89/343/EEC; Council Directive 89/381/EEC; Council Directive 92/26/EEC; Council Directive 92/27/EEC; Council Directive 92/73/EEC; and Regulation (EEC) No. 2309/93 and any Regulations adopted by the Commission under Article 15.4 or 22.1 of that Regulation." [429]

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[426]"Message of the French Presidency of the Council of the European Union on the occasion of the inauguration of the European Agency for the Evaluation of Medicinal Products. London, 26 January 1995." Issued as a press release by the Agency.
[427] MCA (1994g).
[428]Ibid.
[429]Regulation 1(2) of the 1994 Regulations.

The MCA summarised the effect of the 1994 regulations:

" The Regulations will mainly affect the human use pharmaceutical industry. Many of the companies concerned operate multinationally and stand to gain from the enhanced marketing potential across the Community. There will be no significant change to the data requirements for companies submitting applications, nor to the assessment criteria of safety, quality and efficacy. Changes to the system will be largely procedural, and will introduce greater flexibility for pharmaceutical companies in terms of the licensing options open to them. It should become easier and cheaper for a company to bring a product onto the market in more than one Member State." [430]

The framework of the 1994 Regulations is as follows:

Section 1	Citation, commencement and interpretation.
Section 2	Responsibility for Member States' functions under the Regulations and Directives.
Section 3	Marketing authorizations for relevant medicinal products.
Section 4	Applications for the grant, renewal or variation of a United Kingdom marketing authorization.
Section 5	Consideration and grant or refusal, of an application for, or for renewal or variation of, a United Kingdom marketing authorization.
Section 6	Revocation, suspension or variation of a United Kingdom marketing authorization or the suspension of the use or marketing of medicinal products.
Section 7	Obligations of holders of marketing authorizations, and offences by holders of marketing authorizations and other persons.
Section 8	Control of retail sale or supply of relevant medicinal products.
Section 9	Consequential and other amendments of the Act and the Medicines Act 1971.
Section 10	Application of enforcement provisions of the Act.
Section 11	Other Schedules to have effect.
Schedule 1	Exemptions and exceptions from the provisions of Regulation 3.

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[430]MCA (1994g).

Schedule 2 Procedural provisions relating to the grant renewal, variation, revocation and suspension of United Kingdom marketing authorizations.

Schedule 3 Offences, Penalties etc.

Schedule 4 Modifications of enforcement provisions of the Act.

Schedule 5 Labels.

Schedule 6 Transitional provisions.

Schedule 7 Consequential amendments to Regulations.

The MCA issued guidelines on the operation of the 1994 Regulations and concluded that the main controls of the Regulations related to:

" • application requirements and procedures for the grant, variation and renewal of UK product licences (henceforth to be known as UK marketing authorizations, the term which appears in the Regulations);

• obligations imposed on holders of UK marketing authorizations, including in particular pharmacovigilance requirements;

• requirements relating to labelling and package leaflets;

• provisions relating to action by the licensing authority to suspend, compulsorily vary or revoke a marketing authorization;

• related enforcement measures." [431]

The Regulations replace the product licence, labels and leaflets provisions of the Medicines Act. However, the Medicines Act remains the legal basis for manufacturers' licences, wholesale dealers' licences, controls on sale and supply and controls on promotion.[432]

In effect, the 1994 Regulations set out the framework for the decentralised procedure; Regulation 2309/93 sets out the framework for the centralised procedure and this Regulation is implemented by the 1994 Regulations.

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[431]MCA (1995i) p4.
[432]Ibid.

3.6.3 The Licensing System under the 1994 Regulations

Regulation 2 of the 1994 regulations states that unless otherwise specified,

> " In so far as they relate to relevant medicinal products and fall to be performed by, or by any authority of, the United Kingdom, the functions of a Member State, or of the competent authority of a Member State, under any of the relevant Community provisions shall [...] be performed by the licensing authority."

As was stated earlier in this Chapter,[433] the provisions of the Medicines Act are therefore continued and the responsibility for licensing medicinal products remains with the Licensing Authority.[434]

Regulation 3 of the 1994 Regulations sets out the requirement to hold a marketing authorization:

> " Except in accordance with any exception or exemption set out in the relevant Community provisions and subject to paragraphs 1 and 3 of Schedule 1 -
>
> (a) no relevant medicinal product shall be placed on the market; and
>
> (b) no such product shall be distributed by way of wholesale dealing,
>
> unless a marketing authorization in respect of that product has been granted in accordance with the relevant Community provisions by the licensing authority or the European Commission, and is for the time being in accordance with those provisions."

The definition of "relevant medicinal product" is discussed in Chapter Four.[435] Exemptions and exceptions from the requirement to hold a marketing authorization are set out in Schedule 1 to the 1994 Regulations and in Article 2 of Directive 65/65/EEC.[436]

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[433] p100.
[434] Section 6(1) and Section 1(1)(a) and (b) of the Medicines Act 1968.
[435] p181.
[436] "3. Chapters II to V shall not apply to:

Regulation 4 of the 1994 Regulations sets out the details relating to applications for the grant, renewal or variation of a United Kingdom marketing authorization[437]: and Article 4 of Directive 65/65/EEC states that such applications must be accompanied by the various "particulars and documents". Article 1 of Directive 75/319/EEC specifies that these "particulars and documents" should be drawn up by experts with the necessary technical or professional qualifications and Article 2 sets out the duties of these experts. Directive 75/319/EEC sets out the procedure for the examination of an application. Article 1 of Directive 75/318/EEC specifies that the "particulars and documents" must be submitted in accordance with the Annex to this Directive.

- medicinal products prepared on the basis of a magistral ["Any medicinal product prepared in a pharmacy in accordance with a prescription for an individual patient." Article 1, paragraph 4.] or official formula ["Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question." Article 1, paragraph 5.],
- medicinal products intended for research and development trials,
- intermediate products intended for further processing by an authorized manufacturer

4 A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from Chapters II to V medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients on his direct personal responsibility."

[437] "(1) Every application for the grant, renewal or variation of a United Kingdom marketing authorization for a relevant medicinal product shall be made in accordance with the relevant Community provisions, subject to any provision of Community law affecting parallel imports, and the applicant shall comply with so much of the relevant Community provisions as impose obligations on applicants as are applicable to the application or the consideration of it.

(2) Every application shall be made in writing, shall be signed by or on behalf of the applicant and shall, unless the licensing authority otherwise direct, be accompanied by any fee which may be payable in connection with that application.

(3) In the case of an application for the grant of a marketing authorization, twenty-six copies, or such lesser number as the licensing authority may direct, of each application and of any accompanying material shall be supplied to the licensing authority in the English language, and where the application or any accompanying material has been translated from another language, also one copy of the application or the accompanying material, as the case may be, in the original language. [...]

(5) An application for the grant of a marketing authorization shall include a statement indicating -

(a) whether the relevant medicinal product is one that should be available
  (i) only on prescription;
  (ii) only from a pharmacy; or
  (iii) on general sale; and

(b) what, if any, provisions of the authorization are proposed concerning the method of sale or supply of the product (including, in particular, any proposed restrictions affecting the circumstances of the use or promotion of the product). [...]

(8) The applicant for the grant or renewal of a United Kingdom marketing authorization must be established in the Community."

When making an application for a marketing authorization, applicants must also take account of the guidance relating to the administrative requirements of the application dossier published by the Commission in the "Notice to applicants for marketing authorizations for medicinal products for human use in the European Union"(December 1994)[438] and the guidance relating to the structure and content of the dossier published in the "Notice to applicants for marketing authorization for medicinal products for human use in the Member States of the European Community" (January 1989).[439] The applicant must also take account of the Community guidelines relating the safety, quality and efficacy of medicinal products issued by the CPMP and listed in Appendix V.

Paragraph 5 of the 1994 Regulations sets out the requirements relating to the grant, renewal and variation of marketing authorizations. In relation to the suspension, variation or revocation of marketing authorizations, Paragraph 6 of the 1994 Regulations states that:

> " The licensing authority may and, where appropriate shall, subject to and in accordance with the relevant Community provisions, revoke, suspend or vary a marketing authorization for a relevant medicinal product."

Article 11 of Directive 65/65/EEC states that a marketing authorization will be suspended :

> " where that product proves to be harmful in the normal conditions of use, or where its therapeutic efficacy is lacking, or where its qualitative and quantitative composition is not as declared. Therapeutic efficacy is lacking when it is established that therapeutic results cannot be obtained with the proprietary product.

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[438]Commission (1994)
[439]Commission (1989b) pp48-176.

An authorization shall also be suspended or revoked where the particulars supporting the application as provided for in Articles 4 and 4a are incorrect or have not been amended in accordance with Article 9a, or when the controls referred to in Article 8 of this Directive or in Article 27 of Second Council Directive 75/319/EEC of 20 May 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products have not been carried out."

Diagrams 1 and 2 set out flow charts showing how the centralised and decentralised procedures operate in practice.[440]

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[440] These diagrams are taken from the Future Systems document prepared by the MCA (1993I).

Diagram 1

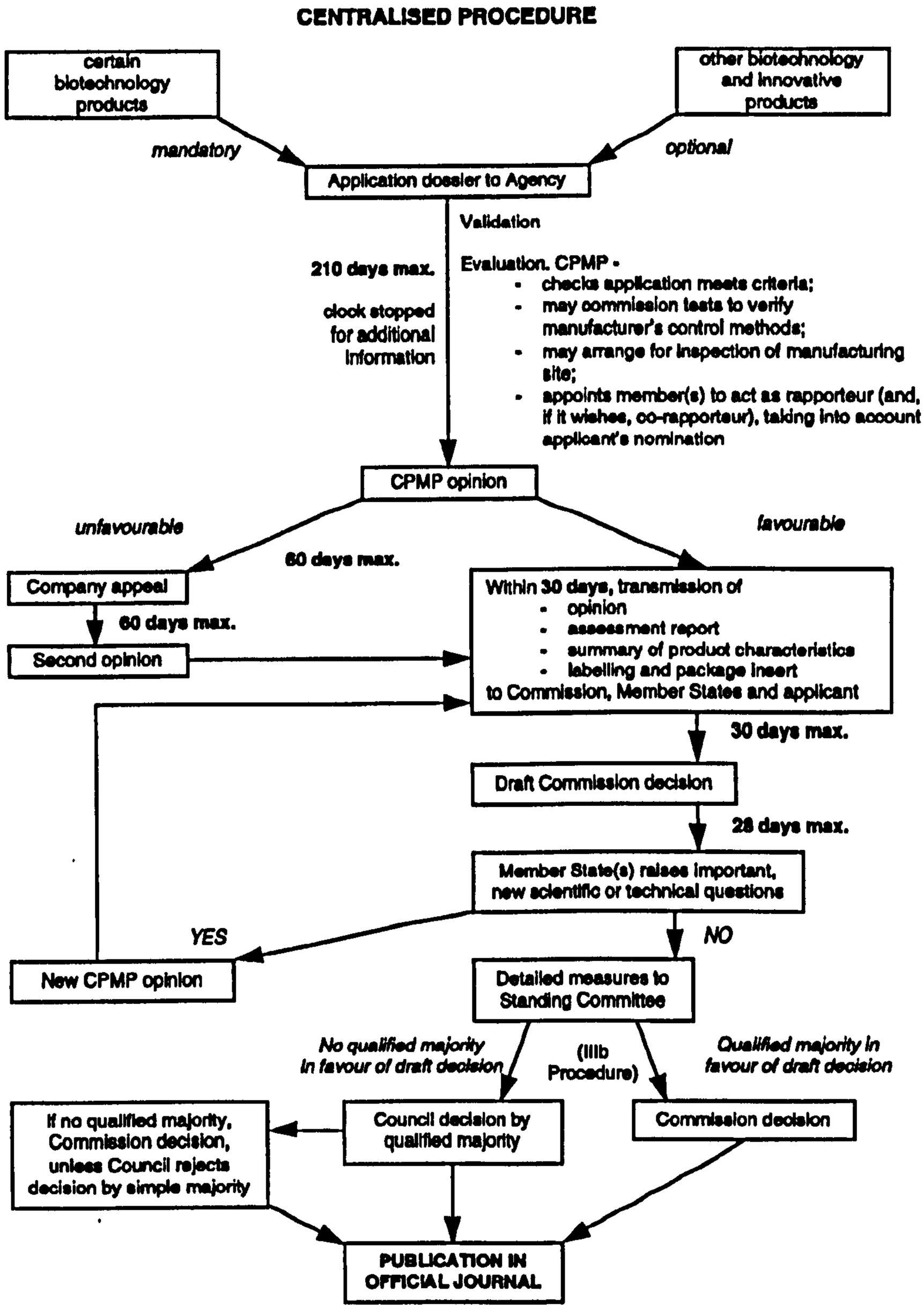
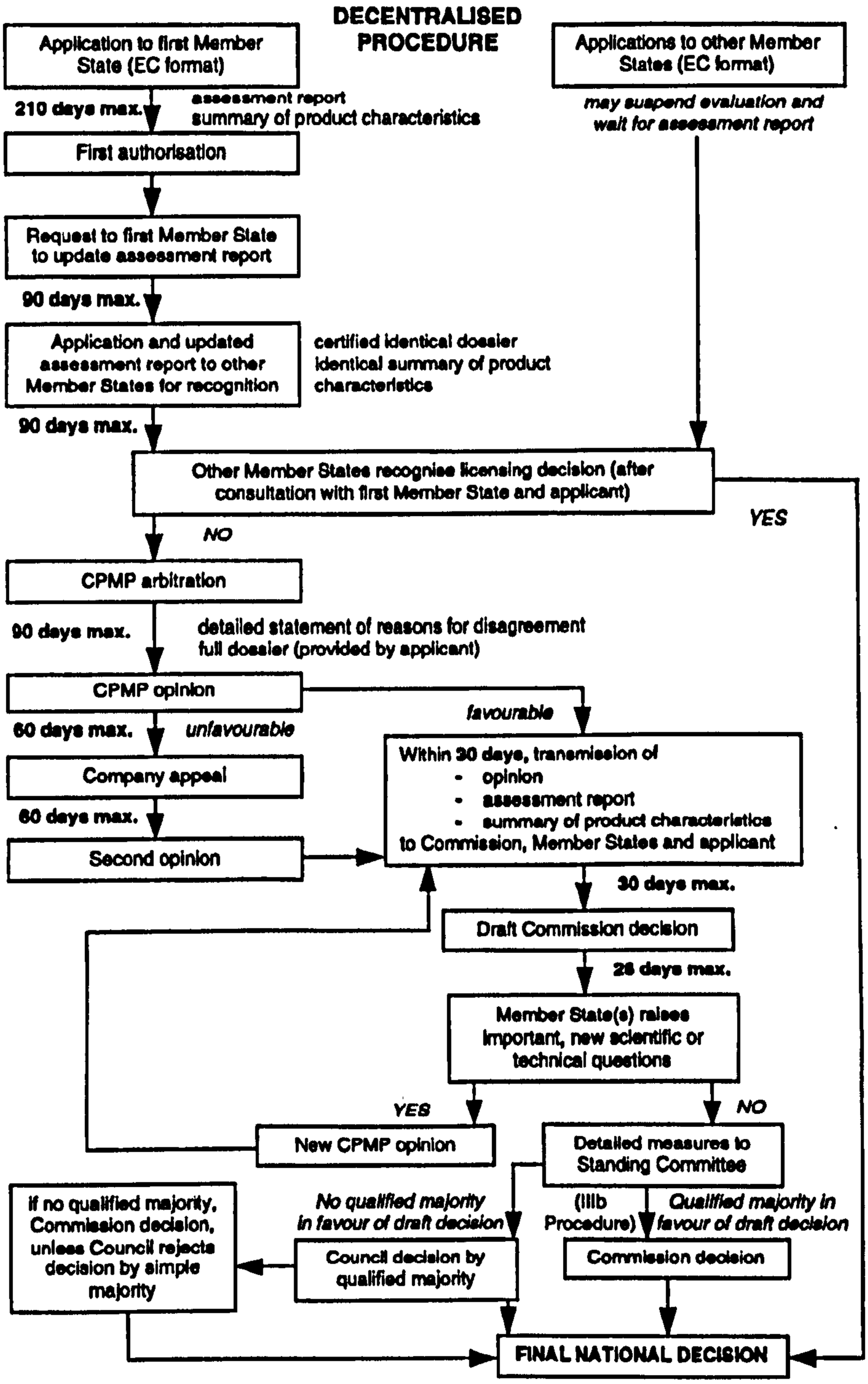

CENTRALISED PROCEDURE
certain biotechnology products
other biotechnology and innovative products
mandatory
optional
Application dossier to Agency
Validation
210 days max.
clock stopped for additional information
Evaluation. CPMP -
checks application meets criteria;
may commission tests to verify manufacturer's control methods;
may arrange for inspection of manufacturing site;
appoints member(s) to act as rapporteur (and, if it wishes, co-rapporteur), taking into account applicant's nomination
CPMP opinion
unfavourable
favourable
60 days max.
Company appeal
60 days max.
Second opinion
Within 30 days, transmission of
opinion
assessment report
summary of product characteristics
labelling and package insert
to Commission, Member States and applicant
30 days max.
Draft Commission decision
28 days max.
Member State(s) raises important, new scientific or technical questions
YES
NO
New CPMP opinion
Detailed measures to Standing Committee
No qualified majority in favour of draft decision
(IIIb Procedure)
Qualified majority in favour of draft decision
If no qualified majority, Commission decision, unless Council rejects decision by simple majority
Council decision by qualified majority
Commission decision
PUBLICATION IN OFFICIAL JOURNAL

Diagram 2


DECENTRALISED PROCEDURE
Application to first Member State (EC format)
Applications to other Member States (EC format)
210 days max.
assessment report
summary of product characteristics
may suspend evaluation and wait for assessment report
First authorisation
Request to first Member State to update assessment report
90 days max.
Application and updated assessment report to other Member States for recognition
certified identical dossier
identical summary of product characteristics
90 days max.
Other Member States recognise licensing decision (after consultation with first Member State and applicant)
YES
NO
CPMP arbitration
90 days max.
detailed statement of reasons for disagreement
full dossier (provided by applicant)
CPMP opinion
favourable
60 days max.
unfavourable
Company appeal
60 days max.
Second opinion
Within 30 days, transmission of
- opinion
- assessment report
- summary of product characteristics
to Commission, Member States and applicant
30 days max.
Draft Commission decision
28 days max.
Member State(s) raises important, new scientific or technical questions
YES
NO
New CPMP opinion
Detailed measures to Standing Committee
if no qualified majority, Commission decision, unless Council rejects decision by simple majority
No qualified majority in favour of draft decision
(IIIb Procedure)
Qualified majority in favour of draft decision
Council decision by qualified majority
Commission decision
FINAL NATIONAL DECISION

As stated earlier, in relation to the administration of the 1994 Regulations, the Medicines Control Agency, Medicines Commission, Committee on Safety of Medicines and the British Pharmacopoeia Commission all continue to work in the manner described in section 3.5.4 above. A new administrative body, the European Agency for the Evaluation of Medicinal Products (EMEA), was established by Regulation 2309/93.[441] The EMEA is based in London and commenced operation on 1 January 1995. It is responsible for overseeing the operation of the centralised and decentralised licensing procedures.

Article 51 of this Regulation sets out the objectives of the EMEA:

> " In order to promote the protection of human and animal health and of consumers of medicinal products throughout the Community, and in order to promote the completion of the internal market through the adoption of uniform regulatory decisions based on scientific criteria concerning the placing on the market and use of medicinal products, the objectives of the Agency shall be to provide the Member States and the institutions of the Community with the best possible scientific advice on any question relating to the evaluation of the quality, the safety and the efficacy of medicinal products for human or veterinary use, which is referred to it in accordance with the provisions of Community legislation relating to medicinal products."[442]

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[441] Article 49.

[442] "To this end, the Agency shall undertake the following tasks within its Committees:
(a) the co-ordination of the scientific evaluation of the quality, safety and efficacy of medicinal products which are subject to Community marketing authorization procedures;
(b) the transmission of assessment reports, summaries of product characteristics, labels and package leaflets or inserts for these medicinal products;
(c) the coordination of the supervision, under practical conditions of use, of medicinal products which have been authorized within the Community and the provision of advice on the measures necessary to ensure the safe and effective use of these products, in particular by evaluating and making available through a database information on adverse reactions to the medicinal products in question (pharmacovigilance);
(d) advising on the maximum limits for residues of veterinary medicinal products which may be accepted in foodstuffs of animal origin in accordance with Regulation (EEC) No. 2377/90;
(e) coordinating the verification of compliance with the principles of good manufacturing practice, good laboratory practice and good clinical practice;
(f) upon request, providing technical and scientific support for steps to improve cooperation between the Community, its Member States, international organizations and third countries on scientific and technical issues relating to the evaluation of medicinal products;

The EMEA comprises:

> (a) the Committee for Proprietary Medicinal Products, which shall be responsible for preparing the opinion of the Agency on any question relating to the evaluation of medicinal products for human use;[443]
>
> (b) the Committee for Veterinary Medicinal Products, which shall be responsible for preparing the opinion of the Agency on any question relating to the evaluation of veterinary medicinal products;
>
> (c) a Secretariat, which shall provide technical and administrative support for the two committees and ensure appropriate coordination between them;
>
> (d) an Executive Director, who shall exercise his responsibilities set out in Article 55;
>
> (e) a Management Board, which shall exercise the responsibilities set out in Articles 56 and 57."[444]

Article 52 sets out requirements relating to: the appointment of members to the CPMP; co-ordination of the tasks of the Agency and the work of competent national bodies; reliance on the scientific assessment and resources available to the national marketing authorization bodies; and scientific consensus. The current members of the CPMP are listed in Appendix XIV.

At present, the CPMP has five Working Parties: Biotechnology; Efficacy; Pharmacovigilance; Safety; and Quality.[445]

(g) recording the status of marketing authorizations for medicinal products granted in accordance with Community procedures;
(h) providing technical assistance for the maintenance of a database on medicinal products which is available for public use;
(i) assisting the Community and Member States in the provision of information to health care professionals and the general public about medicinal products which have been evaluated within the Agency;
(j) where necessary, advising companies on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products." Article 51 ibid.

[443]The CPMP was established by Directive 75/319/EEC. However, its functions were amended substantially by Directive 93/39/EEC to take account of the new licensing procedures.

[444] Article 50.

[445]Ibid p19.

The current Executive Director of the EMEA is Dr. Fernand Sauer. Article 55 states that the Executive Director is the legal representative of the Agency and sets out his responsibilities.[446]

- the draft annual accounts for the previous year,

Article 56 contains provisions relating to the Management Board. The Board consists of two representatives from each Member State, two representatives of the Commission and two representatives appointed by the European Parliament. The term of office is 3 years and this is renewable. The current members of the Management Board are listed in Appendix XIV.

Further aspects of the new regulatory scheme will be discussed in Chapter Four.[447]

3.7 Conclusions

With the benefit of hindsight, the Author finds it surprising that, prior to thalidomide, earlier opportunities for a review of the legislation relating to medicinal products, such as the inter-departmental working party set up in 1959 and the reports by Discombe and the WHO[448], had been missed. It also seems surprising that, following thalidomide, it took so long before the Medicines Act 1968 was drafted and then implemented. Also, it took more than 30 years before the provisions of Directive 65/65/EEC were implemented into UK law by the 1994 Regulations. Admittedly,

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446 " - for the day-to-day administration of the Agency,
- for the provision of appropriate technical support for the Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products, and their working parties and expert groups,
- for ensuring that the time limits laid down in Community legislation for the adoption of opinions by the Agency are respected,
- for ensuring appropriate co-ordination between the Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products,
- for the preparation of the statement of revenue and expenditure and the execution of the budget of the Agency,
- for all staff matters." Article 55 ibid.

447 For example, p158.

448 As discussed in Section 3.5.1 earlier in this Chapter.

these various UK and European legislative provisions were complicated, but one would have thought that legislation could have been in force quicker.

Since the introduction of the Medicines Act 1968, there has been criticism of its "effectiveness". In 1982, Hartley and Maynard published a report based on information gathered from questionnaires which they had sent out to 25 pharmaceutical companies (16 questionnaires were returned). Hartley and Maynard in assessing the "costs" of the 1968 Act,[449] questioned whether the 1968 Act was worthwhile and considered alternatives to the 1968 Act.[450] They concluded by saying:

> " The point to be made is that the present regulatory system has its deficiencies, with doubts about its social desirability. Nor is the present system the only solution: there exists a range of alternatives. In the circumstances of mounting criticisms and genuine doubts about the value of the 1968 Medicines Act, we would argue that now is the time for a serious re-appraisal of the UK's regulatory arrangements."[451]

Certainly, prior to the publication of this report there had been problems related to delays associated with applications for Clinical Trial Certificates. In 1981, a clinical

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[449] " (a) The Act absorbs over 1000 staff (full-time equivalents) in industry and Government.
(b) The Act has led to delays in the marketing of new drugs, possibly an extra two years or more. Such an increase has to be related to a trend towards lengthier development periods, currently requiring some 10 years for a new product.
(c) There has been an adverse effect on innovation (i.e. fewer new drugs are marketed). This, together with delays, has had harmful effects on patients."
(d) UK-owned firms reported a decline in the proportion of their R&D undertaken in the UK.
(e) The licensing authority takes almost 10 months to handle CTC applications and about one year for product licences. These time periods have increased due to:
(i) a shortage of qualified licensing authority staff;
(ii) increased regulatory requirements
(f) Documents submitted to the licensing authority are substantial volumes. The combined applications for a CTC and a Product Licence exceeds 4000 pages and requires over 8 months of preparation at a cost of £35,000.
(g) The total cost of these effects could be £25-28m per annum (1979 prices), and this is a conservative estimate. In other words, expressed in 1981 prices the Act could be costing the community more than £30m per year (with an upper limit in the region of £85m per annum)." Hartley and Maynard (1982) p34

[450] Ibid.

[451] Ibid p35

trial exemption scheme was established in order to alleviate the delays.[452] Speirs and Griffin examined the effect of the new scheme and commented:

> " The results of this survey indicate that the number of new chemical entities submitted for clinical evaluation has increased two-fold in the first year of operation of the scheme compared with the average of the last 3 years. The scheme has operated at no increased hazard to the patients participating in the clinical studies."[453]

It was not until 1987 that the problems associated with bureaucracy within the Medicines Division and delays relating to product licensing were investigated by Evans and Cunliffe.[454]

Other criticisms made by Hartley and Maynard have been overtaken by the developments in Europe and the acceptance that there was to be a pan-European system of regulation.

Since the publication of Hartley and Maynard's report, the Institute for Economic Affairs published a paper "Medicines in the Marketplace" which proposed the adoption of

> " a less rigid approval mechanism similar to the original Committee on Safety of Drugs."[455]

However, generally speaking, following the introduction of the Clinical Trial Exemption scheme and the establishment of the Medicines Control Agency, there has not been criticism of the entire legislative framework, more that improvements

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[452] S.I. 1981/164. See also Chapter 12 in Griffin, ed. (1992), Speirs and Griffin (1983), Griffin and Stewart (1988) and Griffin and Long (1981) for background details on this problem.
[453] Speirs and Griffin (1983) p654.
[454] As discussed in Section 3.5.4 earlier in this Chapter.
[455] Green (1987) p61.

could be made to certain aspects. In Chapter Four, the Author discusses aspects of the current framework, which could be amended.[456]

It is the opinion of the Author that the main difficulty with the legislative framework is that it is too unwieldy. For example, the Medicines Act 1968 has been amended by over 300 statutory instruments, the 1994 Regulations and many European Directives (which have also been amended). It is suggested by the Author that the current legislative framework consisting of the great variety of sources discussed in this Chapter, should be consolidated into a single piece of legislation. Although it is appreciated by the Author that this would be a complex drafting exercise, it is nevertheless crucial as it would clarify a number of ambiguities which have crept into the interpretation of the Medicines Act following the implementation of the 1994 Regulations, particularly in relation to the status of Part II of the Medicines Act. Statutory instruments will continue to amend the new legislative framework, but it is suggested by the Author that each new statutory instrument should consolidate earlier statutory instruments. Certainly, a recent consolidation exercise has been carried out in relation to prescription only medicines and the Prescription Only Medicines (Human Use) Order 1997 was implemented earlier this year.[457] It consolidated 17 statutory instruments, but it has already been amended.[458]

In this Chapter, the development of the legislative framework following thalidomide was discussed. In Chapter Four, the Author will focus on problems encountered in current practice under the legislative framework which potentially affect the three elements of the hypothesis: pharmaceutical innovation, consumer safety and legal redress.

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[456]For example, p192.
[457] S.I. No. 1997/1830.
[458] S.I. No. 1997/2044.

Chapter Four

An Analysis of Current Practice under the Legislative Framework as it affects Pharmaceutical Innovation, Consumer Safety and Legal Redress

Part I

Impact of the Legislative Framework on Pharmaceutical Innovation

4.1 Introduction

In Chapter 1, pharmaceutical innovation was identified as the most important area of effort for research-based pharmaceutical companies and that expenditure on pharmaceutical research development amounts to more than £2 billion per year.[459] It takes 10 to 12 years to develop a new medicinal product and this process costs more than £200m.[460] It is widely regarded that the introduction of new medicinal products is beneficial not only to patients but also to the economy.[461] Therefore, it important that pharmaceutical innovation leading to the introduction of new medicinal products is not hindered by the legislative framework.

In its Annual Review for 1996, the ABPI articulated the following concerns relating to pharmaceutical innovation:

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[459] p8.
[460] ABPI (1991c) and (1996).
[461] OHE (1995).

> " The long-term, high-investment, high-risk nature of innovation by the pharmaceutical industry demands stable policies to ensure fair and adequate commercial returns. The industry needs to be especially vigilant in the protection of vital intellectual property rights and in mitigating the problems of parallel trade."[462]

The ABPI also stated that:

> " Government policies during recent years have resulted in a decline in the fabric of our centres of education and in the funding of university and Research Council sponsored research. In view of the importance of the science base to the industry, the ABPI will continue to emphasise to the Government the need for increased investment in the science infrastructure of the UK, focusing the limited resources available while recognising the crucial importance of investment in long-term research discovery."[463]

The Centre for Medicines Research International has published a series of articles dealing with pharmaceutical innovation in the UK.[464] These articles have dealt with issues of concern such as patent erosion and attrition rates. These issues relate to matters which are outwith the scope of this thesis. The CMR has stated that:

> " Patents are essential for the pharmaceutical industry and the importance of appropriate patent term and protection as the stimulus to innovative medicines research is unquestionable."[465]

The Director-General of the ABPI, Dr Jones, has commented that:

> " The cost of research and development (R&D) in pharmaceuticals is high. If such R&D is to continue in the UK, as well as in the European Community, then there must be an adequate return on investment from successful products.

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[462] ABPI (1997) p13
[463] Ibid p14.
[464] Walker and Parrish (1986), Lumley et al (1987 and (1989), Prentis et al (1988) and Lis and Walker (1989). For further discussion relating to patents see Jones et al (1989), ABPI (1990c) and (1990d), EFPIA (1988) and McKenna (1990).

The adequacy of the patent life of pharmaceutical products is important for both research-based and generic companies, since without novel medicines there would be no new generics.

However, the very special products of the pharmaceutical industry's endeavours, as distinct from ordinary items of commerce, do not enjoy the benefits of a reasonable patent life, as this is mostly spent in the necessary evaluation of compounds for acceptability, in terms of safety, quality and efficacy."[466]

As far as pharmaceutical innovation is concerned, it is suggested by the Author that, from an industry perspective, issues such as patent protection and the decline in the university science base are believed to have a greater impact on innovation than the regulatory requirements imposed by the Medicines Act 1968 and associated European Directives.

Utilising the research techniques outlined throughout Chapter Two, no reports were found in the medical, scientific or legal materials which claimed that specific medicinal products had not been introduced because of excessive regulation or threat of legal action in the UK; this contrasts with the USA, where litigation has allegedly delayed the introduction of products such as oral contraceptives[467] and vaccines.[468] Certainly in the past (as discussed in the Chapter Three[469]), certain aspects of licensing, specifically applications for clinical trial certificates, delays at Medicines Division and delays in the multi-state and concertation licensing procedures were of concern to the pharmaceutical industry in relation to innovation. The Author could not find evidence of recent industry complaints relating to the legislative framework.

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[465] CMR (1989) p3.
[466] Ibid p5
[467] Tyres and Salas (1989), Weiss (1987) and Mastroianni et al (1990)
[468] Soloway (1989).
[469] pp149-150.

However, what is of concern is that the centralised and decentralised licensing procedures may degenerate into bureaucratic and complicated licensing systems. An encouraging development is the Government's Deregulation Initiative, which aims to reduce the administrative burden on business by "removing unnecessary controls and eliminating duplication."[470] This initiative has affected the MCA and it has been reviewing the way in which regulations operate:

> " The aim is to reduce excessive burdens on business without compromising public health or safety. A central principle is that regulations should be fully justified and proportionate to the risk of harm which they are intended to control. Task forces were set up to advise Ministers on priorities for the repeal or simplification of existing regulations so as to minimise the costs on business. The Chemicals and Pharmaceuticals Deregulation Task Force identified clinical trial authorisation as an area of regulation that could be simplified. [...] Patient safety has not been compromised by these matters." [471]

The new proposals were implemented by The Medicines (Exemptions from Licences)(Clinical Trials) Order 1995[472] and The Medicines (Exemptions from Licences and Certificates (Clinical Trials) Order 1995.[473] These proposals replace the clinical trial exemption scheme established in 1981 mentioned in the previous chapter.[474]

It is suggested by the Author that a measure of the bureaucracy of a licensing system is the length of time it takes for a medicinal product to be licensed. This is an

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[470]MCA (1993L).
[471]Ibid.
[472]S.I. 1995/2808.
[473]S.I. 1995/2809. The MCA has published guidance on these new regulations, "Guidance Notes on Applications for Clinical Trial Exemptions and Clinical Trial Certificates". [MCA (1996)].
[474]S.I. 1981/164. See also Chapter 12 in Griffin, ed. (1992), Speirs and Griffin (1983), Griffin and Stewart (1988) and Griffin and Long (1981). See p149.

area of research which has occupied researchers in the USA.[475] Commenting on what came to be referred to as the "drug lag", the BMJ reported:

> " Despite official claims to the contrary, valuable drugs have been partially or wholly denied to the American people for long periods. Critics have argued that the United States Food and Drug Administration has been depriving rather than protecting the public or even cynically avoiding risk by waiting to see what happens elsewhere."[476]

For a while in the USA, there was justifiable concern about delays and the Food and Drug Administration (FDA) introduced initiatives to speed up the new drug approval process primarily in response to the demand for access to investigational treatments for AIDS and the fast-track development of new products for AIDS.[477] Comparisons were made between the USA and UK, and it was concluded that there were more medicinal products available in the UK than in the USA.[478] However, more recently the former Director of the FDA stated that licensing times in the USA and the UK are now the same.[479]

The next section will analyse the operation of the centralised and the decentralised licensing systems. However, because these new licensing systems have been operating for only a short time, it may be too early to analyse the full impact of these new systems.

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[475] Di Masi et al (1991), Scheck et al (1984), Mattison et al (1988), Reidenberg (1990), May et al (1983), Young (1982), Rumore (1992), Spivey (1985), Wardell et al (1980) and Wardell et al (1982). See also Parker (1989), Pieterson (1992) and Finkel (1991).

[476] BMJ (1980a).

[477] Kaitin and Walsh (1992), Edgar and Rothman (1990), Mariner (1990), Marlin (1989), Roberts and Biggers (1989), Will (1990), Power (1987), Wachster (1992), Mattison (1988), Scoville (1991), Booth (1981), Marwick (1988), Young et al (1988), Eaglstein (1988), Kaitin (1991), Kahan and Read (1990), Kessler (1989), Foreman (1991), Marshall (1989), Cochetto (1989), Stone (1990) and Schofield (1992).

[478] For example, Kaitin et al (1989).

[479] Woods (1996).

4.2 An Analysis of the Operation of the Decentralised and Centralised Licensing Procedures

In the UK, the centralised and decentralised licensing procedures came into operation in January 1995, as was discussed in Chapter 3.[480] Initially, these new systems had to deal with outstanding applications under the multi-state and concertation procedures, as well as new applications.[481] In its first general report, the EMEA stated that in its first year of operation it had received 30 applications under the centralised procedure and 30 applications under the decentralised procedure subject to mutual recognition.[482]

In its Annual Report for 1996, the CSM stated that it had received a total of 156 applications for marketing authorisations.

> " An increasing part of the Committee's work has been devoted to giving advice on applications made through the new European procedures. The Committee has been consulted on a significant number of incoming mutual recognition applications including all those involving new chemical entities. The Committee is pleased to note the high proportion of mutual recognition applications for which the United Kingdom is the reference Member State. Many of the applications which the Committee considered earlier in the calendar year have now successfully completed the mutual recognition procedure."[483]

The CSM also reported that it had given advice on five new active substances covering 15 EC centralised marketing authorisations for which the United Kingdom was either the rapporteur or co-rapporteur.[484]

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[480] p140
[481] EMEA (1996a). The multi-state and concertation procedures are discussed in Chapter 3 at pp .
[482] Ibid.
[483] Medicines Commission et al (1997) p15.
[484] Ibid.

In its Annual Report 1996/97, the MCA reported that it had assessed 39 new active substances during the year in a mean time of 43 days. Last year, the MCA had assessed 47 new active substances in a mean time of 51 days.[485] The MCA further commented that it had committed significant resources to assist in the development of the Mutual Recognition procedure and had become the leading Reference Member State.[486] The MCA also reported that it had been appointed as rapporteur or co-rapporteurs for 13 centralised applications and that the UK was one of the major rapporteurs or co-rapporteurs.

In relation to centralised applications, there have been no reports of delays in the time taken to process these types of applications, despite an increase in the number of applications in 1996.[487] In addition, in a limited number of applications for medicinal products used in the treatment of serious disease, the EMEA has been able to accelerate the time taken to evaluate these types of products.[488]

On 21 October 1996, the "Second Conference on the New European Marketing Authorisation System" took place. In relation to the centralised procedure, the Chairman of the CPMP commented that he felt it had been a "real success":

> " The number of applications was encouraging. All CPMP opinions so far had been positive and adopted by consensus, showing a willingness on the part of members and national experts to work together. The number of voluntary applications (List B - innovative medicines) was felt to be an additional indication that the procedure was a success."

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[485] MCA (1997f) p7.
[486] Ibid p9.
[487] EMEA (1997a) p23.
[488] Ibid.

However, two main areas of difficulty in relation to the centralised procedure were identified. These related to trademarks and committee procedures.[489] The EMEA also identified the following areas where improvements could be made:

- **a rapid Community mechanism for dealing with urgent cases where public health is at risk is required to allow a speedy scientific evaluation of the case and adoption of an opinion, leading to a legally binding speedy Commission decision.**
- **each individual step of the normal centralised procedure must be reviewed to enhance efficiency, including rapid transmission of EMEA opinions to the Commission and streamlining of the Commission's decision-taking procedure.[490]**

Appendix XVIII lists all the medicinal products which have been licensed under the centralised procedure and details the therapeutic areas involved, the manufacturers responsible and the time taken to licence these products. In terms of Art 6(4) of Regulation 2309/93, an opinion of the Committee must be given within 210 days. However, the clock can be stopped in periods where information is being sought from the applicant. It can be seen from this Appendix that there have been some products which have exceeded this 210 days period; some delay has been attributed to the Committee having to deal with applications originating from the concertation procedure.[491]

In relation to the decentralised procedure and the mutual recognition procedure, there have been more serious delays reported with regard to the processing of applications, and the EMEA stated that:

- **" The first year had proved difficult for both national competent authorities and industry, but that these difficulties could only be resolved through more applications being made."[492]**

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[489] EMEA (1996r)
[490] Ibid
[491] Information taken from EMEA (1997n) and (1997o).
[492] Inid.

In addition, the EMEA stated that various problem areas had been identified:

- long delays were experienced between the successful outcome of mutual recognition and the granting of national marketing authorisations.
- the need for IT support to bring transparency to the functioning of mutual recognition.
- firm commitment needed from national authorities to go to arbitration only where necessary and where public health issues were involved.
- specific difficulties were being experienced by the generic medicines industry, although the situation regarding the so-called 'reference product' and bioequivalence studies had been clarified at recent meetings in Brussels.[493]

In order to counter these problems, a "Best Practice Guide" was adopted by national Competent Authorities (such as the MCA) to improve the operation of these application procedures.[494] The EMEA also decided to improve confidence in these procedures and promote transparency, by introducing an IT tracking system to monitor the progress of applications. It was considered by the EMEA that legislative adjustments to the application procedures could only be made once there was "sufficient experience".[495]

Following the initial problems reported by the EMEA, Table 24 illustrates that the use of the Mutual recognition procedure has increased.

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[493] Ibid.
[494] Ibid.
[495] Ibid.

Table 24 Decentralised Applications using the Mutual Recognition Procedure (1995 - 1997)

Year	New Applications finalised	Type I variations finalised	Type II variations finalised	Arbitrations referred to CPMP
1995	10	16	17	1
1996	84	49	73	2
1997	113	75	94	2

In 1997, Treece published an article comparing the new licensing procedures with the US FDA. In his article, he included information from a survey of pharmaceutical companies which had used these new procedures. This article was of particular interest to the Author as it was the first to examine the operation of the new licensing procedures. Treece stated that there were advantages to the new procedures over the FDA's licensing procedures. He concluded that:

> " **If there is one major fault in the system, it will be the perennial fault of the variation in standards between the Competent Authorities of the Member States. Whilst there is no evidence at the moment to show that there is a wide variation in the standards for testing and accepting of drugs between the Competent Authorities, the in-built competitiveness of the rapporteur system raises the possibility that drug manufacturers will tend to gravitate towards Member States whose Competent Authorities have a reputation for a high percentage of approvals. There needs to be a system to ensure that some states do not inflate their approval rates (possibly to the detriment of doing a full and accurate evaluation) in order to attract business. If this were to occur it would have the effect of bringing the whole of the European regulatory system into disrepute. Whilst it would be relatively easy to ensure that such an eventuality can not arise by having the EMEA act as a licensing standards body to ensure that the same**

> **standards of evaluation are adhered to throughout the EU, this is a step that the EU have been generally reluctant to take."[496]**

The Author agrees with Treece that variations in standards between the Competent Authorities of the Member States would be a problem. However, as is stated by Treece and confirmed by the Author's own research, there is no evidence of this problem developing. The UK is the leading reference state and one of the major rapporteurs or co-rapporteurs for these licensing procedures,[497] and there has been no reported criticism of the MCA as having dropped its evaluation standards to inflate its approval rates in order to attract more applications.

Contrary to the suggestion made earlier that licensing times in the UK and the USA are now the same, and that there is no drug lag in the USA,[498] Treece has suggested that the USA has failed to achieve a balance between taking a reasonable time to license a medicinal products while at the same time ensuring that the product has been tested carefully. Treece suggests that the European licensing framework "attempts to manage" this balance.[499]

A joint EMEA/EFPIA press release issued on 23 October 1997, reported on a seminar held between industry and regulatory officials, "Performance Review of the European Registration System". The press release stated that a number of areas for improvement were identified, which included:

> **" Issues at the time of the oral explanations, the quality of the translations as well as the mechanism for their submission and assessment, clarification of questions from the CPMP, the avoidance of slippage and the time taken by companies to respond to these questions."[500]**

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[496] Treece (1997) pp332 - 333.
[497] MCA (1997f) p9.
[498] p157.
[499] Ibid. p333.
[500] EMEA (1997o) p8.

In addition, the press release reported that:

> " The CPMP Chairman referred to a general need for companies to be more focused during oral explanations and lack of professionalism in exceptional cases. From an operational perspective, companies expressed the wish for time-tables to be more strictly adhered to and greater privacy when preparing for oral explanations. [...]

However, the overall attitude was positive and all parties expressed their commitment to continue to work together towards better performance. EMEA and EFPIA have already organised a series of work-shops aiming to resolve many of these issues, the results of which will be made public."[501]

The main difficulty in assessing the operation of the centralised and decentralised procedures, is that there has just not been enough experience with these new procedures to conclude how effectively they are operating. However, it would appear, as evidenced from the recent seminar in October, that regulatory officials and the pharmaceutical industry are working together to achieve an efficient regulatory system. Also, Treece's review shows encouraging indications and certainly there have been no reports in the medical press of complaints from the industry relating to delays in licensing.

4.3 Conclusions

The Author concluded that pharmaceutical innovation must be encouraged and that it was important that the introduction of new medicinal products should not be hindered by the legislative framework.

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[501] Ibid.

The difficulties in assessing the impact of the current legislative framework on pharmaceutical innovation are threefold. First, no published reports were found in the medical, scientific or legal materials consulted, which claimed that specific medicinal products had not been introduced in the UK because of excessive regulation or threat of legal action. Second, the Author could not find evidence of there having been any recent industry complaints relating to the legislative framework, although there have been complaints in the past regarding the former licensing system under the Medicines Act 1968. Third, there has just not been enough experience with the new centralised and decentralised procedures to conclude how efficiently the legislative framework is operating.

On the basis of what evidence is available, the Author, suggests that the operation of the current legislative framework would not appear to have been so overly bureaucratic as to have had a negative impact on pharmaceutical innovation.

Part II

Impact of the Legislative Framework on Consumer Safety

4.4 Introduction

Chapter One surveyed a number of withdrawals of medicinal products for safety reasons and reports of serious adverse reactions to medicinal products since Thalidomide.[502] It was further discussed that no medicinal product is safe and it is a question of assessing the risks of treatment as against the benefits. The assumption is that threats to consumer safety originate from design defects in medicinal products; what may not be appreciated is that there is a risk to consumers from a variety of sources.

There could be threats to consumer safety from fraud and misconduct in medical research[503] or counterfeit medicinal products.[504] In its most recent annual report, the MCA reported there had been 209 reports of defective medicinal products and it was acknowledged that these manufacturing defects could have had potential

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[502] pp11-12.
[503] Lock and Wells (1993), Smith (1996), Evered and Lazar (1995), Wells (1992), Hove (1993) and Lancet (1997d).

implications for consumer safety.[505] There are also risks from herbal and homeopathic products; this is discussed in the next section. Adverse reactions can occur to excipients in medicinal products such as colouring agents, preservatives, sweeteners, tablet and capsule binders, antioxidants, emulsifying, solubilising and wetting agents, perfumes, ointment bases and solvents.[506]

Consumers are also at risk from health frauds and the US Food and Drug Administration have identified the "Top Ten" frauds as being:

" 1. Fraudulent arthritis products, such as copper bracelets, Chinese herbal remedies, megadoses of vitamins, and snake or bee venom;
2. spurious cancer clinics;
3. bogus AIDS cures;
4. instant weight-loss schemes;
5. fraudulent sexual aids;
6. quack baldness remedies and other appearance modifiers;
7. false nutritional schemes, including the use of products such as bee pollen, herbal remedies, and wheat-germ capsules;
8. chelation therapy (use of an amino acid to break down arterial plaque);
9. use of muscle stimulators to remove wrinkles, perform face lifts, reduce breast size, and eliminate cellulite; and
10. remedies for candidiasis hypersensitivity, such as anti-fungal drugs and vitamin and mineral supplements."[507]

Consumers are also at risk from deliberate or accidental overdoses and misuse of medicinal products. The Royal Pharmaceutical Society of Great Britain has prepared a list of substances available from pharmacies which have been misused.

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[504] Moran (1993), Ten Ham (1992) and Pharmaceutical Journal (1987dd). For example, counterfeit Ventolin and Zantac has been discovered in the UK - Pharm J (1989aa), (1989bb) and (1990x)
[505] MCA (1997f) p23.
[506] Smith and Dodd (1982), Scott (1990), Golightly (1988a) and (1988b).
[507] Am J Hosp Pharm (1990).

" **Non-medicinal products**

1. **All products containing solvents, or propellants.**

   For example, Glues, Tippex, nail varnish remover, Dylon conditioner, PR spray, Zoff, methylated and surgical spirits, butane gas refills, cleaning fluids aerosols, Ralgex and Deep Freeze sprays.

2. **Chemicals**

   For example, Citric acid, ascorbic acid (used to convert street heroin into a more soluble form for intravenous injection), amyl nitrite, isobutyl nitrite, benzyl methyl ketone, ergot alkaloids (precursors), acetic anhydride, allylbenzene and acetonitrile.

Pharmacy Medicines

1. **Any combination of codeine, ephedrine, morphine, antihistamine or similar substances.**

   For example, Veganin, Do-Do, Phensedyl, codeine linctus, Gees linctus, Pulmo Bailly, Day Nurse, Night Nurse, Medinite, kaolin and morphine mixture, Dimotane Co, Feminax

2. **Antihistamines alone**

   For example, Avomine, Dramamine, Phenergan, Medinex, Nytol, Nytol One-a-Night.

3. **Cyclizine preparations**

   For example, Valoid, Femigraine

4. **Laxatives (misused by anorexics)**

   For example, Dulcolax, Micralax Sodium phosphate, Ex-Lax, Nylax and Senokot

5. **Sympathomimetics**

   For example, Sudafed, Actifed

6. **Ephedrine, pseudo ephedrine and phenyl propanolamine**

   For example, Mucron, Sinutab [508]

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[508] Royal Pharmaceutical Society (1997).

Consumers are at potential risk from any breach of the regulations relating to the control of medicinal products. In its Annual Report for 1996/97, the Enforcement Group of the MCA reported that they had investigated 234 cases in which a breach of the Medicines Act 1968 was alleged. 90% of these allegations were found to be accurate: 63% were resolved by advice, warnings or formal caution and the remainder were prosecuted (convictions were obtained in all of these cases).

> " The Agency investigated a wide variety of cases ranging from counterfeit medicines, illegal manufacture, mail order selling, wholesale dealing without a licence, illegal retail sale and illegal dispensing. [...] The Group also investigating three emerging areas of concern to public health: the growth of business activities with traditional Chinese medicines, the Internet and the increasing sale as a soft drug of products containing amyl nitrates ('poppers')."[509]

Schedule 3 of the 1994 Regulations sets out offences in relation to marketing authorisations.

Consumers are also at risk from prescribing errors made by doctors[510] and dispensing errors made by pharmacists.[511] In *Dwyer v Roderick*,[512] blame was apportioned between the prescribing doctor and the pharmacist because a prescription for Migril had been prescribed with the incorrect dosage and the pharmacist had not spotted the error. In P*rendergast v Sam & Dee Ltd and others*,[513] blame was again apportioned between the prescribing doctor and the pharmacist, in circumstances where the doctor's handwriting had been so illegible that the pharmacist had misread "daonil" instead of "amoxil". It was held that the pharmacist should have realised that this was not the medicinal product which the doctor intended to prescribe.

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[509] MCA (1997f) p10.
[510] Ferner (1995). Brown (1992), Ferner (1992) and Neville et al (1989).
[511] Pharmaceutical Journal (1996b), Samuels (1996) and Kayne (1996a), (1996b) and (1996c).
[512] (1982) unreported (QBD).

In relation to prescribing errors, Sir Derrick Dunlop commented:

> "The medical profession has not been entirely guiltless in their use of drugs. We must confess that there has been a good deal of excessive and occasionally ignorant and irresponsible prescribing for which there are many reasons.
>
> Firstly, there are too few doctors in most countries for their increasing populations, so that most are busy and some overworked. Although it takes a long time to elucidate an accurate clinical history, to carry out a careful, physical examination, and to give wise advice, it only takes a moment to write a prescription which often satisfies both patient and doctor that some positive action has been taken. [...]
>
> Secondly, ignorant prescribing may often be due to inadequate instruction about drugs. [at university] [...]
>
> Thirdly, excessive prescribing may be encouraged by the insistent and skilful promotion of drugs by the pharmaceutical industry, some of which, in the past at any rate, has been subject to justifiable criticism."[514]

The British National Formulary (BNF) gives advice to doctors on the prescribing of medicinal products and suggests that adverse reactions may be prevented as follows:

> " 1. Never use any drug unless there is a good indication. If the patient is pregnant do not use a drug unless the need for it is imperative.
>
> 2. It is very important to recognise allergy and idiosyncrasy as causes of adverse drug reactions. Ask if the patient had previous reactions.
>
> 3. Ask if the patient is already taking other drugs *including self-medication*; remember that interactions may occur.
>
> 4. Age and hepatic or renal disease may alter the metabolism or excretion of drugs, so that much smaller doses may need to be described.
>
> Pharmacogenetic factors may also be responsible for variations in the rate of metabolism, notably of isoniazid and the tricyclic antidepressants.

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[513] (1989) The Times, 14 March (CA).
[514] Dunlop in Davies (1991).

5. Prescribe as few drugs as possible and give very clear instructions to the elderly or any patient likely to misunderstand complicated instructions.
6. When possible use a familiar drug. With a new drug be particularly alert for adverse reactions or unexpected events.
7. If serious adverse reactions are liable to occur, warn the patient."[515]

Specific advice is also given in the BNF regarding interactions with multiple medicinal products, pregnancy, breast-feeding, liver disease, renal impairment, children, pallitative care, the elderly.

However, Ferner has commented:

" Drug errors are avoidable but difficult to avoid. The prescriber has to be knowledgeable enough to choose an effective treatment suitable for the individual patient, taking into account age, infirmity, and possible interactions with other drugs. Having selected the right agent and the correct dose, the prescriber has to transmit the message to the dispenser, who has then to hand the drug to the patient or to a carer or nurse, who has to see that the drug is given in the correct way and at the specified times. The process is complex, and, not surprisingly, errors occur. As with air travel, deaths are sufficiently rare that 'near misses' are important. More important still is to devise a strategy for reducing errors. Bates et al have recently reported a study from Boston in which they identified about 6.5 actual and 5.5 potential adverse drug events - errors or adverse reactions involving drug treatment - per 100 hospital patients."

In 1996, the Medical Defence Union (MDU) published a report, "Problems in General Practice - Medication Errors". The MDU stated in this report that in a 6 year period in the UK, they opened 21,500 files relating to claims against GP members. They analysed the 790 claims which had settled and found that 25% of

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[515] BMA and Royal Pharmaceutical Society (1991) p10.

these claims (the largest proportion) related to errors in prescribing, monitoring or administering medicinal products. The MDU further stated that in just under half of these settled claims, the injury caused was permanent (e.g. scarring, nerve damage, or cerebrovascular accident) and in 18% of these claims, the medication error resulted in death, stillbirth or a termination of pregnancy.[516]

The six most common reasons for medication errors were as follows:

- incorrect/inappropriate dosage
- contra-indicated medication
- administration error
- prescribing/dispensing errors
- prescribing to patients with a known allergy
- wrong drug.[517]

In 1996, Kayne reviewed dispensing errors by pharmacists in a series of articles published in the Pharmaceutical Journal and commented:

" A general practitioner can write a prescription incorrectly and the pharmacist, as the last link in the health chain, is seen by patients to be in a position to monitor it and take appropriate action. However, if a pharmacist dispenses the wrong medicine and/or interprets the dose incorrectly, the error could conceivably result in the patient's death. Under these circumstances money would be poor recompense. Finding out what went wrong may be the main reason for relatives of a patient who has died taking action, and may be more important to them than money alone.

Despite claiming that health professionals make fewer mistakes than others - it has been estimated that pharmacists make errors on about 3 per cent of the millions of prescriptions they dispense, although a small survey carried out in

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[516] MDU (1996) p1.

> Glasgow shows that the figure could be considerably less - the potential cost in terms of human suffering is such that their standards will always be expected by the public to be at the highest level."[518]

Kayne concluded:

> " Identifying doctors' errors should not obscure personal inadequacies. The small survey carried out in Glasgow showed that by far the biggest source of potential actions for negligence was straight dispensing errors - picking the wrong bottle or choosing the wrong strength, errors in interpretation, errors in labelling. Although computers have made an enormous difference, it is humans who manipulate their key boards. The adoption of self audit checklists for dispensing, similar to that made available by the Greater Glasgow Health Board and the Scottish National Audit Facilitators, would enable activities to be monitored efficiently on a regular basis and serve to highlight those areas where danger lurks."[519]

It is the opinion of the Author that the risks to consumer safety from health fraud, counterfeit medicinal products, prescribing, errors, dispensing errors, misconduct in medical research, herbal products, homeopathic medicinal products, excipients, and accidental or suicidal overdoses should be researched in greater detail. Some of these risks involve issues which are not controlled by the regulatory framework relating to medicinal products, which has been examined in this Thesis.

In Chapter One, the Author mentioned that, since thalidomide, there have been a number of well-publicised withdrawals of medicinal products and medical devices for reasons of safety, reports of serious adverse reactions and claims for compensation in relation to these adverse reactions.[520] In Table 25, the Author has

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[517] Ibid pp2-3.
[518] Kayne (1996a) p 654.
[519] Kayne (1996c) p35.
[520] pp11-12.

presented a selection of these medicinal products and medical devices, all of which have raised general concern as to how well consumers are protected from injury.

Information on the medicinal products featured in this table has been drawn from miscellaneous articles, books and publications, and from the Committee on Safety of Medicines' publications listed in Appendix VIII.[521]

Table 25 gives an insight into the manner in which certain medicinal products and medical devices were withdrawn . From the information contained in this Table, the Author determined that the experiences associated with these medicinal products could illustrate possible failings in the regulatory system. The Author has used these examples to determine the following specific criticisms of the regulatory system, which will be examined in greater detail later in this chapter: the definition of medicinal product (including herbals and medical devices), conflicts of interest, the legal status of medicinal products, information to patients, promotion and pharmacovigilance.

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[521]Also, Sneader (1985).

Table 25 Medicinal Products and Medical Devices which have been the Subject of a Well-Publicised Withdrawal for Reasons of Safety, or Reports of Serious Adverse Reactions or Claims for Compensation.

Benoxaprofen (Opren) Lilly Industries Ltd (Dista Products Ltd) POM	
1980	Licensed. A non-steroidal anti-inflammatory drug indicated in the treatment of rheumatoid arthritis and osteoarthritis.
1982	Dear Doctor Letter (3 August): "This letter is to inform you that the Licensing Authority has suspended the product licences for Opren with immediate effect on grounds of safety. The suspension is in force initially for a period of three months under the terms of the Medicines Act 1968. This means that the product may not be promoted or supplied by the licence holder, Lilly Industries Limited, (Dista Products) while the suspension is in force. The Committee on Safety of Medicines has received over 3500 reports of adverse reactions associated with this drug; included among these reports are 61 fatal cases, predominantly in the elderly. Having regard to these reports there is concern about the serious toxic effects of the drug on various organ systems, particularly the gastro-intestinal tract, the liver, and bone marrow, in addition to the known effects on skin, eyes and nails."
1982	Product Licences voluntarily surrendered by the licence holder (11 September). CSM Annual Report: "The Committee had been monitoring this drug carefully since it was first marketed in 1980 and had considered the problems of skin sensitivity to sunlight and gastrointestinal bleeding in 1981 when a very large number of yellow card reports of skin reactions associated with the drug had been received. The Committee saw some evidence in October 1981 on the handling of the drug in the elderly, presented by the company as a possible explanation of the serious gastro-intestinal effects in some elderly patients. This evidence was conflicting, and the Committee considered it to be an inadequate basis for a reduction in recommended dosage for elderly patients. The Committee continued to monitor the drug carefully. From May 1982 evidence began to appear of serious liver and kidney damage associated with the drug, particularly in elderly people. In May the Committee recommended a reduction in dosage for the elderly. This was a precautionary measure in case accumulation of the drug was the cause of serious adverse effects in the elderly. After the first alert in the British Medical Journal, reports of deaths from jaundice associated with the drug increased rapidly. By late July, reports in the professional journals and to the Committee relating to serious adverse reactions and deaths associated with the drug indicated that the hazard of the drug outweighed the benefits.

Table 25 contd.

1982 contd.	The Committee therefore advised the Licensing Authority that the product licences be suspended immediately and this was done on August 4. The Committee has been much criticised for its handling of the problem, but considers that it acted correctly in recommending suspension of the drug only when the scientific evidence justified it. The yellow card adverse reaction reporting system provided the confirmatory evidence that was necessary before such action could be taken against the product. The Committee accepts that the yellow card system has limitations - in particular, early warnings of possible drug adverse effects are generally more quickly picked up in medical journals - but considers that it does provide useful evidence on adverse reactions to drugs and it proved its value in this case. [...] The Committee has set up a working party on adverse reactions to consider if it can improve the way it fulfils its role in the important field of adverse reaction monitoring."
1987	Eli Lilly's offer of settlement was announced - £2,275,00 to be divided among 1200 plaintiffs. Many other plaintiffs were time-barred from pursuing legal action.
Criticisms	• The Yellow Card Scheme for the reporting of adverse reactions. • The manner in which the announcement of the withdrawal was made. • Alleged conflict of interest - the Chairman of the CSM was involved in early clinical trials. • Inadequacy of clinical trials. • Marketing in the medical press and in the general press. • Prescribing practices. • The system of legal redress. • Alleged clinical trial fraud
Benzodiazepines **Including diazepam, lorazepam, temazepam and triazolam** Various manufacturers	
1960s	Introduced. Used as anxiolytics and hypnotics.
1988	Current Problems 21: "There has been concern for many years regarding benzodiazepine dependence (Br Med J 1980: 280, 910-912). Such dependence is becoming increasingly worrying. Withdrawal symptoms include anxiety, tremor, confusion, insomnia, perceptual disorders, fits, depression, gastrointestinal and other somatic symptoms. These may sometimes be difficult to distinguish from the symptoms of the original illness. It is important to note that withdrawal symptoms can occur with benzodiazepines following therapeutic doses given for SHORT periods of time. Withdrawal effects usually appear shortly after stopping a benzodiazepine with a short half life, or up to several days after stopping one with a long half life. Symptoms may continue for weeks or months. No epidemiological evidence is available to suggest that one benzodiazepine is more responsible for the development of dependency or withdrawal symptoms than another."

Table 25 contd.

1989-1991	More than 17,000 patients brought legal action over alleged adverse reactions.
Criticisms	• Prescribing practices. • Information given to patients. • The system of legal redress. In particular, problems were experienced with legal aid and the operation of the group action.
Convexo-Concave (C-C) Heart Valves Bjork-Shiley	
1990	Current Problems 30: "The 60° Bjork-Shiley convexo-concave valve, manufactured in the USA, was first introduced into the UK in 1979. It was used either in the aortic or mitral position and was originally marketed in seven sizes. A number of incidents of failure related to strut fracture were reported. From 1982 the manufacturer progressively withdrew certain models and in 1986 stopped all manufacture and supply on a world-wide basis. Some 82,000 of 60° convexo-concave (c-c) valves were implanted world-wide before distribution ceased. There have been approximately 300 failures, of which about two thirds were fatal. The most recent data from the manufacturer on the statistical risk of mechanical failure indicates that this lies between 0.02 and 0.3 per cent per year depending on the size of the valve and the date of manufacture. In the United Kingdom approximately 5,000 60° c-c valves were implanted. There have been 36 confirmed reports of failure and 28 patients have died. Over a period of several years the overall failure rate recorded in this country is thus 0.7 per cent. No specific cause has been found to explain why a small percentage of these valves experience strut fracture and there is currently no reliable method of predicting which valves are going to fail. In this country, the operative mortality of valve replacement is about 5 per cent, whereas as indicated the risk of strut fracture of the 60° c-c valve is about 0.7 per cent. Between 1982 and 1983, 43 Bjork-Shiley 70° convexo-concave valves were implanted into UK patients taking part in a clinical trial. One mechanical failure has been reported. The manufacturer has reported mechanical failures of either 0.22 or 0.6 per 100 patients per year for those batches of 70° c-c valves implants implanted in the UK. A group of 70° c-c valves at higher risk of strut fracture was identified by the manufacturer but none of the valves implanted in the UK belonged to this group. Acute failure of artificial heart valves is discussed in an article by Professor K. Taylor in the British Medical Journal. Elective re-operation is not currently recommended. The Department of Health's Medical Directorate advises that: Any patient with an implanted 60° and 70° Bjork-Shiley convexo-concave valve, who is not regularly followed up, should be referred for assessment to a consultant cardiologist or cardiothoracic surgeon. The diagnosis of acute structural failure should be suspected in any patient known to have an artificial heart valve who suddenly develops severe cardiac failure. The patient should be referred immediately for consideration of re-operation."
1991	Current Problems 31: "Up to April 1991, there have been 39 confirmed reports of failure [of 60° c-c valves] of which 30 patients died. Over a period of several years the overall failure rate recorded in this country is thus 0.78 per cent. The risks of re-operation remain considerably greater than that of strut fracture."

Table 25 contd.

1992	Shiley offered a settlement totalling $155 to 205 million, to 55,000 people worldwide who have the valve. Compensation is being sought for the constant fear that the valve may fracture and result in death
Criticism	• Heart valves are not controlled by the Medicines Act 1968. (Now controlled by Devices Regulations).
Iophendylate (Myodil)	
Glaxo	
POM	
1945	Introduced. A radio-opaque, ionic contrast medium used in x-rays of the spinal cord.
1960s - 1980s	Reports of patients suffering arachnoiditis following injection with Myodil.
1987	Withdrawn by manufacturer.
1995	Out of court settlement of £7 million.
Criticisms	• Inadequate clinical trials. • Inadequate patient information.
Paracetamol and Aspirin	
1899	Aspirin introduced.
1953	Paracetamol introduced.
1986	Dear Doctor Letter (10 June): "The Committee has considered available evidence on possible links between Reye's syndrome and aspirin use by feverish children and recommend that aspirin should no longer be given to children aged under 12 years, unless specifically indicated, for example, for juvenile rheumatoid arthritis. Reye's syndrome is a rare acute encephalopathy associated with fatty change of the liver. The major clinical features include severe vomiting and impaired consciousness which may progress rapidly to delirium and coma. It occurs typically after viral infections such as influenza or chickenpox. UK experience points to an annual incidence here of between 3 and 7 cases per million children under 16 years. Reye's syndrome can sometimes be managed successfully in hospital, but mortality in Britain has been about 50%, and some survivors have brain damage. In the USA, four case control studies published between 1980 and 1982 were said to show a positive association between aspirin use and Reye's syndrome. However, the studies generated considerable scientific controversy and a further study, designed to eliminate possible sources of error, was mounted by the US Public Health Services in 1983. The pilot phase of this study provided evidence to support a possible association between Reye's syndrome and aspirin use by feverish children. In the light of these findings, the US Food and Drug Administration and the manufacturers of aspirin-containing medicines warned parents against giving aspirin to children and teenagers with influenza or chickenpox. Subsequently fewer children in the US received aspirin for these conditions and the incidence of Reye's syndrome declined significantly.

Table 25 contd.

1986 contd.	In the UK, a Reye's Syndrome Surveillance Scheme set up jointly by the British Paediatric Association and the Public Health Laboratory Services Communicable Diseases Surveillance Centre received reports of 229 cases of Reye's syndrome in the British Isles in the four years between August 1981 and the end of July 1985. The preliminary results of a risk factor study (which is not yet completed)undertaken as part of the Scheme are in line with the US experience of a possible association between Reye's syndrome and aspirin use. The Scheme indicates that the epidemiology of Reye's syndrome in Britain differs from that in the USA. The age of onset here (median 14 months) appears to be substantially lower than in the US and 93% of reported British cases relate to children aged under 12 years. No evidence has been presented pointing to an association between paracetamol use and Reye's syndrome. The Committee has considered the available evidence and concluded that, while the causes of Reye's syndrome are not clearly defined, aspirin may be a contributory factor to the causation of Reye's syndrome in some children. Since paracetamol is an effective alternative treatment for fever in children we consider that it is prudent to avoid giving aspirin to children under 12 years unless specifically indicated. Aspirin is usually given to children as an over-the-counter medicine by parents who do not think medical attention is needed. It is therefore important for doctors and other health professionals to advise families that aspirin is not, on the evidence now available , a suitable medicine for children with minor illnesses. The Committee has welcomed steps being taken voluntarily by the pharmaceutical industry to inform the public about the risks of giving aspirin to children: (i) paediatric aspirin products will be withdrawn from sale; (ii) press advertisements will advise parents not to give aspirin to children under 12 (iii) adult aspirin labels will be changed, by early 1987, to warn against giving aspirin to children; (iv) posters will be available from family practitioner committees and health authorities for display in GP surgeries, pharmacies and child health clinics."
1997	Current Problems (October): "Measures are being introduced over the coming year to reduce the use of paracetamol and aspirin in deliberate and accidental overdose. Paracetamol overdose overdose now accounts for 30-40,000 hospital admissions and 100-150 deaths each year; aspirin overdose is responsible for around 5,000 admissions and 50 deaths. To limit availability and reduce residual stocks in the home, packs of these analgesics will be limited to 16 tablets or capsules through general sales outlets such as supermarkets, and 32 tablets or capsules through pharmacists. Larger quantities for chronic conditions can be provided up to a total of 100 tablets or capsules at the discretion of a pharmacist. Above this quantity a prescription will be required. These restrictions do not apply to effervescent forms, granules, powders, suppositories and liquids, as these are seldom implicated in overdose. In addition, warnings about overdose will be included on the labels and leaflets for paracetamol products. Patients can be reassured that when used correctly, paracetamol and aspirin are both safe and effective."
Criticisms	• Legal status of medicinal products. • Information supplied to patients. • Adverse reaction monitoring of over-the-counter products.

Table 25 contd.

Practolol (Eraldin) ICI POM	
1970	Introduced
1975	Adverse Reactions Series 11 (January): "By the end of 1974, 187 reports had been received of adverse effects on the eye occurring in patient who have been treated with practolol ("Eraldin"). Two-thirds of these reports described diminished tear secretion and conjunctivitis, and the remainder, corneal damage leading on occasion to impairment or loss of vision. These effects on the eye have been noted in patients who have received practolol for periods ranging from a few weeks to several years. There are also several hundred reports of psoriasiform or hyperkeratotic skin reactions and 25 patients have complained of deafness. Fourteen patients have developed a syndrome resembling systemic lupus erythematosus and 8 have developed an unusual form of sclerosing peritonitis. Half the patients with eye changes had a rash and in others these adverse reactions were multiple. The mild eye changes and the majority of skin reactions usually recover when practolol has been withdrawn, but the outcome with corneal involvement is less certain and the damage may be irreversible. In some patients it has been reported that the abrupt cessation of practolol may lead to a worsening of angina and to cardiac arrhythmia. [...] In view of the serious and unusual nature of these reactions patients who need to continue to receive long-term treatment with practolol should be carefully observed with a view to the early detection of adverse reactions."
1975	Current Problems 1 (September): "The number of reported serious adverse reactions associated with practolol continues to increase. More than 20 cases of sclerosing peritonitis have now been reported. The Committee wishes to emphasise that this condition has sometimes become apparent several months after treatment with practolol has ceased."
1975	Practolol withdrawn from general use.
1976	Current Problems 2: "Prescribers are reminded that the recommended uses of practolol (Eraldin) are restricted to certain acute cardiac dysrrhythmias in hospitalised patients. The Committee cannot, however, be sure that these recommendations are being observed. It is therefore taking this opportunity of reminding doctors that the hazards of practolol make it unsuitable for the treatment of angina or hypertension."
1976	ICI set up a compensation scheme.
Criticisms	• Under-reporting of adverse reactions. • Failure of clinical trials to identify serious adverse reactions. • Medicinal product of value withdrawn from use. • Information supplied to the patients.

4.5 Products which fall outwith the scope of the Legislative Framework relating to Relevant Medicinal Products

4.5.1 Introduction

The Author considered that a possible safety concern for consumers was the scenario whereby products which have been reported to cause adverse reactions were not controlled by the legislative framework. This section examines the definition of "relevant medicinal product" (i.e. those products which are controlled by the current legislative framework). The Author then considers the regulation of homeopathic medicinal products, certain herbal products, medical devices and products supplied on a named patient basis, all of which products fall outwith the definition of "relevant medicinal product".

4.5.2 Definition of "Relevant Medicinal Product"

Regulation 3 of the 1994 Regulations states that "relevant medicinal products" cannot be placed on the market unless they have a UK or a Community marketing authorization. A "relevant medicinal product" is defined as:

> " A medicinal product for human use to which Chapters II to V of Council Directive 65/65/EEC apply, and accordingly includes the industrially produced medicinal products mentioned in Article 2.2 of that Directive."[522]

Article 2 of Directive 65/65/EEC states:

> " 1. Chapters II to V shall apply to proprietary medicinal products for human use intended to be placed on the market in the Member States.

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[522]Regulation 1(2).

A "proprietary medicinal product" is defined as:

> " Any ready-prepared medicinal product placed on the market under a special name and in a special pack"[523]

Directive 65/65/EEC defines "medicinal product" as:

> " Any substance or combination of substances presented for treating or preventing disease in human beings or animals.
>
> Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals." [524]

Appelbe and Wingfield commented that:

> " this is a broader definition than that in the Medicines Act and can be defined as being a medicinal product (a) by presentation and (b) by function."[525]

"Substance" is defined as:

> " Any matter irrespective of origin which may be:
>
> - human, e.g. human blood and blood products.
> - animal, e.g. micro-organisms, whole animals, parts or organs, animal secretions, toxins, extracts, blood products etc.
> - vegetable, e.g. micro-organisms, plants, parts of plants, vegetable secretions, extracts, etc.
> - chemical, e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis."[526]

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[523]Article 1, paragraph 1.
[524]Article 1, paragraph 2.
[525] Appelbe and Wingfield (1997) p2.
[526]Article 1, paragraph 3.

In relation to "industrially produced" products:

> " 2. Where a Member State authorises the placing on the market of industrially produced medicinal products which do not comply with the definition of a proprietary medicinal product, it shall also apply Chapters II to V to them."[527]

Article 34 of Directive 75/319/EEC specified that Chapters II to V of Directive 65/65/EEC did not apply to vaccines, toxins or serums, to medicinal products based on human blood or blood constituents or radioactive isotopes or to homeopathic medicinal products. However, Directive 89/342/EEC extended the provisions of 65/65/EEC and 75/319/EEC to apply to immunological medicinal products for human use consisting of vaccines, toxins or serums and allergens. "Allergen product" is defined as:

> " any product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent." [528]

"Vaccines, toxins or serums" includes:

> " - *agents used to produce active immunity*
>
> (such as cholera vaccine, BCG, polio vaccine, smallpox vaccine)
>
> - *agents used to diagnose the state of immunity*
>
> including, in particular, tuberculin and tuberculin PPD, toxins for the Schick and Dick tests, brucellin
>
> - *agents used to produce passive immunity*
>
> (such as diphtheria, antitoxin, anti-smallpox globulin, antilymphocytic globulin)." [529]

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[527]Directive 65/65/EEC, as amended by 89/341/EEC.
[528]Article 1, 89/342/EEC.
[529]Annex, 75/319/EEC.

Directive 89/343/EEC extended the provisions of 65/65/EEC and 75/319/EEC to apply to radiopharmaceuticals for human use, excluding radionuclides in the form of sealed sources. A "radiopharmaceutical" is defined as

> " any relevant medicinal product which when ready for use contains one or more radionuclides included for a medicinal purpose." [530]

This definition covers generators,[531] kits,[532] precursor[533] radiopharmaceuticals and industrially prepared radiopharmaceuticals.[534] However, the definition does not include:

> " a radiopharmaceutical prepared at the time of use by a person or by an establishment authorized, according to national legislation, to use such medicinal products in an approved health care establishment exclusively from authorized generators, kits or precursor pharmaceuticals in accordance with the manufacturer's instructions." [535]

Directive 89/381/EEC extended the provisions of Directives 65/65/EEC and 75/319/EEC to apply to medicinal products derived from human blood or human plasma which are prepared industrially by public or private establishments. These products include albumin, coagulating factors and immunoglobuins of human origin.[536] However, whole blood, plasma or blood cells of human origin are not included.[537]

According to the MCA, the definition of "relevant medicinal product" includes the "great majority of products hitherto controlled under the Medicines Act".

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[530]Article 1, 89/343/EEC.

[531]Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be removed by elution or by any other method and is to be used in a radiopharmaceutical." Article 2.

[532]"Any preparation to be reconstituted or combined with radionuclides in a final radiopharmaceutical, usually prior to its administration." Article 2.

[533]"A radionuclide produced for the radio-labelling of another substance prior to its administration, other than a radionuclide which is incorporated in or produced from a generator or is included in a radiopharmaceutical." Article 2.

[534]Article 2, 89/343/EEC.

[535]Ibid.

However, a small category of products administered outside the body, such as agents for the preservation of organs intended for transplantation, which were not regulated by the Medicines Act, will now require marketing authorizations.[538]

Article 3 of Regulation 2903/93 sets out the medicinal products for which the centralised procedure is mandatory:

" No medicinal product referred to in Part A of the Annex may be placed on the market within the Community unless a marketing authorization has been granted by the Community in accordance with the provisions of this Regulation."

Part A of the Annex is as follows:

" Medicinal products developed by means of one of the following biotechnological processes:

- recombinant DNA technology
- controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
- hybridoma and monoclonal antibody methods.

Veterinary medicinal products, including those not derived from biotechnology, intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals."

Article 3 of Regulation 2309/93 further states that for certain medicinal products, the centralised procedure is optional:

" The person responsible for placing on the market a medicinal product referred to in Part B of the Annex may request that the authorization to place the medicinal product on the market be granted by the Community in accordance with the provisions of this Regulation."

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[536]Paragraph 1, Article 1.
[537]Paragraph 2, Article 1.
[538]MCA (1995i) p4-5.

Part B of the Annex is as follows:

" Medicinal products developed by other biotechnological processes which, in the opinion of the Agency, constitute a significant innovation.

Medicinal products administered by means of new delivery systems which, in the opinion of the Agency, constitute a significant innovation.

Medicinal products presented for an entirely new indication which, in the opinion of the Agency, is of significant therapeutic interest.

Medicinal products based on radio-isotopes which, in the opinion of the Agency, are of significant therapeutic interest.

New medicinal products derived from human blood or plasma.

Medicinal products, the manufacture of which employs processes which, in the opinion of the Agency, demonstrate a significant technical advance such as two-dimensional electrophoresis under micro-gravity.

Medicinal products intended for administration to human beings, containing a new active substance which, on the date of entry into force of this Regulation, was not authorized by any Member State for use in a medicinal product intended for human use.

Veterinary medicinal products intended for use in food-producing animals containing a new active substance which, on the date of entry into force of this Regulation, was not authorized by any Member State for use in food-producing animals."

Article 3 states that if it is considered to be necessary, Parts A and B will be re-examined by the CPMP in the light of scientific and technical progress and amended.

The MCA has summarised the categories of product which it considers to be excluded from the definition of "relevant medicinal product":

" • medicinal products authorised for clinical trials supply (through Clinical Trial Certificates or the Clinical Trial Exemption Scheme);

• products controlled through orders made under sections 104 and 105 of the Medicines Act;

- products prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia for direct supply to patients, or made up in accordance with a prescription for an individual patient;
- homeopathics registered under the scheme set up in early 1994 by S.I. 1994/105;
- herbal remedies manufactured and sold or supplied in accordance with the exemptions in sections 12(1) or 12(2) of the Medicines Act or Article 2 of the Medicines (Exemptions from Licences)(Special and Transitional Cases)Order 1971 (S.I. 1971/1450)." [539]

According to the MCA, these products and also homeopathic medicinal products with Product Licences of Right will not be covered by the 1994 Regulations. In addition, Regulation 3(2) and Schedule 1 of the 1994 Regulations set out exemptions from the requirement to hold marketing authorisations. Also, medical devices are controlled by a different set of European regulations and a separate licensing body. Whole blood is also not covered by the 1994 Regulations.

Some of these products have had safety problems and, in the opinion of the Author, the exclusion of these products may be problematic. Of particular concern are medical devices, homeopathic medicinal products, herbal products, and products supplied on a named patient basis.

4.5.3 Homeopathic Medicinal Products

The regulation of homeopathic medicinal products has become increasingly important because it has been reported recently that the homeopathic market will

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[539]MCA (1995i) p5.

grow in the UK from £19.7m to between £52.6m and £72.4m over the next 5 to 10 years.[540]

In 1987, the Medicines Commission considered possible options relating to the regulation of homeopathic medicinal products. The Commission stated that although they were not aware of evidence that these products generally presented a safety risk, they considered that, in respect of certain types of homeopathic products, particular attention should be given to ensuring product quality and to examining whether they should be made available on prescription only.[541] The Commission concluded that

> " The first preference would be for a product licensing system which addressed safety and quality and which disregard efficacy. Such a system would not be possible under the Medicines Act as it stands but could be introduced as a result of EC directives."[542]

In 1992, it was stated in the Preamble to Directive 92/73/EEC that the provisions of Directive 65/65/EEC and the Second Directive 75/319/EEC[543] were not always appropriate for the regulation of homeopathic medicinal products. It was further stated that it was considered desirable in the first instance to provide users of these products with a very clear indication of their homeopathic character and with sufficient guarantees of their quality and safety.

On 14 February 1994, The Medicines (Homeopathic Medicinal Products for Human Use) Regulations 1994 implemented part of this Directive[544] and introduced a new regulatory scheme for homeopathic medicinal products. Regulation 3 states:

> " A certificate of registration shall authorise the placing on the market of a homeopathic medicinal product to which these Regulations apply."

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[540] Pharm J (1996d).
[541] Medicines Commission et al (1988) pp4-5.
[542] Ibid.
[543] Subsequently mplmented in the UK by the 1994 Regulations.
[544] 1994/105, as amended by 1994/899. Other parts of this Directive were implemented by 1994/104, 1994/101

The Regulations also set out requirements relating to: the grant of a certificate; quality control; duration and renewal of certificates; suspension and revocation; withdrawal from the market; variation of certificates; and fees.

The MCA issued guidance for manufacturers and suppliers of homeopathic medicinal products and stated that the following products were outside the scope of the Regulations:

" • products for animal use;

- products prepared in accordance with a magistral or officinal formula (i.e.. those prepared in a pharmacy in accordance with a prescription for an individual patient and preparations intended for supply directly to the patient);
- products supplied in response to unsolicited orders, formulated in accordance with the specifications of a doctor and for use by individual patients on the doctor's direct personal responsibility." [545]

The MCA further stated that to be eligible for registration, a homeopathic medicinal product had to satisfy all of the following criteria:

" • It must be prepared from products, substances or compositions called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence of such a description, by any pharmacopoeia used officially in an EC state.[546]

- It must be for oral or external use. (This includes all methods of administration except injections).
- There must be no specific therapeutic indication included in the labelling or in any information relating to the product.
- The product must bear the scientific name of the stock or stocks from which it is prepared and not a proprietary or trade name.

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and 1994/103.
[545]MCA (1994c) p4.

- It must be sufficiently dilute to guarantee safety.
- It must contain no more than one part per 10,000 of the mother tincture, and, where the active principle is a prescription only medicine (POM), it must contain no more than one part per 100 of the smallest dose used in allopathic medicine." [547]

Applications for certificates of registration are made to the MCA.[548] However, the Advisory Board on the Registration of Homeopathic Products, established in 1994,[549] can advise the MCA, if required, on issues relating to the safety or quality of any homeopathic medicinal product. The Advisory Board also hears appeals from companies regarding the refusal, suspension or withdrawal of a certificate of registration.[550] Appendix XIV lists the members of the Advisory Board. The Board has 11 members who include hospital consultants. veterinary practitioners, a community pharmacist and a homeopathic practitioner.

Since it was established, the Advisory Board has considered the following issues:

- control and quality of homeopathic stocks
- control and quality of dosage forms of homeopathic products
- formulation master files
- method of dilution and potentisation
- stability requirements
- homeopathic terminology
- legislative proposals to classify registered products as GSL unless derived from stocks which are controlled drugs or prescription only medicines
- labelling of homeopathic of medicinal products.[551]

In 1995, the Board considered the labelling and nomenclature of complex homeopathic products and suggested that Directive 92/73 relating to homeopathic

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[546]This is the definition of "homeopathic medicinal product" in Regulation 1(2) of 1994/105.
[547]Ibid p5.
[548]Ibid p7.
[549]Established by S.I. 1994/102. This statutory instrument was revoked because of a defect and was replaced by S.I. 1995/309.
[550]MCA (1994c).
[551] Information taken from the Advisory Board's annual reports - Medicines Commission et al (1995), (1996) and (1997).

products did not make adequate provisions. The Board envisaged that there would be:

> " difficulties in choosing an appropriate product name where several stocks were included in one product and agreed that this issue should be drawn to the attention of the European Commission"[552]

Table 26 presents a summary of the work conducted by the Advisory Board.

Table 26 Summary of work completed by the Advisory Board on the Registration of Homeopathic Products (1994 - 1996)[553]

Year	Applications Received	Applications referred to ABRH	Provisional refusal	Grant advised	Grant advised with conditions	Total
1994	25	0	-	-	-	0
1995	24	13	10	0	3	13
1996	54	2	2	0	0	2

The Advisory Board commented that the number of applications receiving during the first full year of operation of the registration scheme was lower than expected; in its second year of operation, the number of applications which required the consideration of the Advisory Board was even lower.[554] It is of concern that the Advisory Board may not been given enough work to do. Part of the Advisory Board's work in 1996, has involved the dissemination of information regarding the registration scheme to practising homeopaths and manufacturers.[555] However, if there is a risk of the Advisory Board being disestablished then its remit should be extended to include the monitoring of unlicensed herbal products, which, as discussed in the next section, are in need of some form of control.

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[552] Medicines Commission et al (1996) p36.
[553] Medicines Commission et al (1996) p45.
[554] Medicines Commission et al (1996 and (1997).
[555] Medicines Commission et al (1997)

The growth in the homeopathic market means that increasing numbers of consumers are being exposed to potential risks. The introduction of the registration scheme is a definite improvement, but it is still too early to comment on whether the scheme will be fully effective in protecting these consumers or whether these products should be covered by a stricter scheme.

4.5.4 Herbal Products

The definition of "relevant medicinal product" includes products which have been "industrially produced". However, paragraph 3 of regulation 1 of the 1994 Regulations provides an exemption for certain herbal products:

> " a medicinal product which is a herbal remedy is not industrially produced if -
>
> (a) it is, or is to be, sold or supplied in circumstances to which either section 12(1) of the Act or Article 2 of the Medicines (Exemptions from Licences)(Special and Transitional Cases) Order 1971 relate and has been manufactured or assembled only for sale or supply in those circumstances; or
>
> (b) the process to which the plant or plants are subjected in producing the product consists only of drying, crushing or comminuting, and the product is, or is to be, sold or supplied only as provided by section 12(2) of the Act."

Section 12 of the Medicines Act states:

> " (1) The restrictions imposed by sections 7 and 8 of this Act do not apply to the sale, supply, manufacture or assembly of any herbal remedy in the course of a business where
>
> (a) the remedy is manufactured or assembled on premises of which the person carrying on the business is the occupier and which he is able to close so as to exclude the public, and

(b) the person carrying on the business sells or supplies the remedy for administration to a particular person after being requested by or on behalf of that person and in that person's absence to use his own judgement as to the treatment required.

(2) Those restrictions also do not apply to the sale, supply, manufacture or assembly of any herbal remedy where the process to which the plant or plants are subjected in producing the remedy consists only of drying, crushing or comminuting, and the remedy is, or is to be, sold or supplied -

(a) under a designation which only specifies the plant or plants and the process and does not apply any other name to the remedy, and

(b) without any written recommendation (whether by means of a labelled container or package or a leaflet or in any other way) as to the use of the remedy."

Originally, it had been proposed that these herbal products would require a product licence.[556] However, after a "concerted campaign" by herbalists, manufacturers and users of herbal medicines, the Government decided to retain the exemption.[557] Nevertheless, there is considerable body of evidence to support the assertion that "natural does not mean safe";[558] even certain herbal teas have serious side effects.[559] The position of the exempted herbal products needs to be re-examined and pilot studies have been set up in a number of European countries to monitor the safety of herbal products.[560]

An interesting recent development in 1996 was the extension of the Yellow Card Scheme for the monitoring of adverse reactions to now include suspected adverse

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[556]Pharm J (1994a).
[557]Pharm J (1994b).
[558]For example, D'Arcy (1991), De Smet (1991), Penn (1983), and Drug and Therapeutics Bulletin (1986).
[559]Bach et al (1989), Snider (1991), Mostefa-Kara et al (1992), Pharm J (1993k) and Pharm J (1995).
[560]Pharm J (1993).

reactions to unlicensed herbal remedies. An article in the "Current Problems in Pharmacovigilance" series explained why the CSM made this decision:

> " This follows a recent report from Guy's Hospital Toxicology Unit on potentially serious adverse reactions associated with herbal remedies. In 9 cases toxicity from heavy metals was confirmed following exposure to traditional remedies from the Indian Sub-Continent. Twenty-one cases of liver toxicity, including two deaths, were associated with the use of traditional Chinese remedies, although no causative agent was identified. Other adverse reactions have been reported in the literature.
>
> Many people see herbal remedies as "safe" or natural" alternatives and do not consider them to be medicines. Others are reluctant to tell their doctors that they have tried a non-conventional remedy.
>
> We have previously requested reports relating to licensed herbal medicines. Broadly, these are products which make medicinal claims or contain industrially manufactured ingredients. We would now also like to receive reports for unlicensed herbal remedies. These consist of dried, crushed or comminuted herbs which do not make medicinal claims. They may be sold or supplied either by a herbal practitioner or be on general sale."[561]

The fact that the CSM has set up this scheme to monitor these suspected adverse reactions is an indication of how seriously they are taking the report from Guy's Hospital Toxicology Unit regarding the cases of liver toxicity and deaths associated with the use of traditional Chinese herbal remedies which are not controlled by the current legislative framework. It is rare for the CSM to comment on products which are not within its strict remit. Other occasions when the CSM has felt obliged to comment have included the recent use of thalidomide on a named patient basis and

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[561] CSM/MCA (1996c).

the serious problems experienced with heart valves.[562] The Author suggests that this involvement of the CSM further underlines the fact that herbal products are not "safe" and that unlicensed herbal products should be brought under the control of the legislative framework.

4.5.5 "Named Patient" Exemptions

This refers to the supply to the patient of medicinal products which do not have marketing authorizations. Schedule 1 to the 1994 Regulations lists "Exemptions and exceptions from the provisions of regulation 3". Paragraph 1 of this Schedule outlines an exemption for doctors and dentists, often referred to as the "named patient" exemption:

> " Regulation 3(1) shall not apply to a relevant medicinal product supplied in response to a *bona fide* unsolicited order, formulated in accordance with the specification of a doctor or dentist and for use by his individual patients on his direct personal responsibility, but such supply shall be subject to the conditions specified in paragraph 2."[563]

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[562] Discussed at p5 and p199. See also CSM (1990d).

[563] Paragraph 2 states that:

" (a) the relevant medicinal product is supplied to a doctor or dentist or for use in a registered pharmacy, a hospital or a health centre under the supervision of a pharmacist, in accordance with paragraph 1;
(b) no advertisement or representation relating to the relevant medicinal product is issued with a view to it being seen generally by the public in the United Kingdom and that no advertisement relating to that product, by means of any catalogue, price list or circular letter is issued by, at the request or with the consent of, the person selling that product by retail or by way of wholesale dealing or supplying it in circumstances corresponding to retail sale, or the person who manufactures it , and that the sale or supply is in response to a *bona fide* unsolicited order;
(c) the manufacture or assembly of the relevant medicinal product is carried out under the supervision of such staff and such precautions are taken as are adequate to ensure that the product is of the character required by and meets the specifications of the doctor or dentist who requires it;
(d) written records as to the manufacture or assembly in accordance with sub-paragraph (c) are made and maintained and are available to the licensing authority or the enforcement authority on request by them or either of them;
(e) the relevant medicinal product is manufactured, assembled or imported by the holder of an authorization referred to in Article 16 of Council Directive 75/319/EEC which relates specifically to the manufacture, assembly or import of relevant medicinal products to which paragraph 1 applies; and
(f) the relevant medicinal product is distributed by way of wholesale dealing by the holder of a wholesale dealer's licence."

Further provisions relating to the supply of these products, including the maintenance of records and the reporting of adverse reactions, are contained in Paragraphs 6 and 7 of the Schedule.

An article in The Drug and Therapeutics Bulletin contained an analysis of the circumstances in which unlicensed medicinal products were prescribed by doctors or licensed medicinal products were prescribed for unlicensed indications.[564] Unlicensed medicinal products fell into four categories:

- products derived from licensed medicinal products and prepared, for example, as low-dose formulations for children, liquid preparations for the elderly or those unable to swallow, or products free of 'sensitising' agents;
- products unrelated to licensed medicinal products, for which a licence has yet to be given;
- products which have been abandoned, suspended, revoked or not renewed; and
- products used in clinical trials.[565]

This article suggested situations in which non-adherence to licensed uses was justified:

- the licensed indications do not reflect current knowledge;
- the indications listed do not include well proven uses of a medicinal product;
- the licensed indications are over restrictive.[566]

It was concluded that the prescriber could be "particularly vulnerable" if the patient was injured.[567] It is extremely important that a doctor should have clinical freedom, but the use of, for example, thalidomide as an unlicensed medicinal product

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[564]Drug and Therapeutics Bulletin (1992).
[565]Ibid.
[566]Ibid.
[567]Ibid.

remains controversial. In February 1997, the CSM issued a safety warning relating to Ticlopidine, which is not licensed in the UK, and reminded doctors that the legal responsibility for the consequences of using this, or any other unlicensed medicine rested with the prescribing doctor.

The Author suggests that the use of unlicensed medicinal products should be subject to greater monitoring or some form of regulation because the fact that the CSM issued one of its rare warnings regarding a product which was outwith its remit is suggestive that the use of Ticlopidine is widespread and that there is great risk to the consumer. It is unclear exactly how many products are prescribed on a named patient basis. This fact alone is of concern. As stated above, thalidomide with its well documented risk of adverse reactions is an example of an unlicensed medicinal product.

Following the analysis in the Drug and Therapeutics Bulletin, it is clear that there are a number of circumstances in which doctors are justified in prescribing on a named patient basis This practice is clearly set to continue and unless these products are brought within the control of the legislative framework, the alternative is that patients and prescribers fall outwith the "protection" of the legislation.[568]

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[568] CSM/MCA (1997a).

4.5.6 Medical Devices

The White Paper "Forthcoming Legislation on the Safety, Quality and Description of Drugs and Medicines" published in 1967, envisaged that medical devices would be brought gradually under the control of the Medicines Act 1968.

> " Those for human use most likely to be affected at a fairly early stage include implants of metal or plastic (e.g. shunts, valves, synthetic arterial grafts, pacemakers), equipment for the introduction or extraction of fluids or substances into or from the human body (e.g. transfusion and perfusion equipment, syringes, catheters, dialysis systems, needles), surgical dressings, materials used in conservative, orthodontic and prosthetic dentistry, and certain classes of items offered for sale as 'sterile'."[569]

However, the majority of these medical devices remained outwith the control of the Medicines Act and, in 1982, the Committee on Dental and Surgical Materials commented:

> " It appeared anomalous to the Committee that great effort should be spent on contact lens fluids whilst products which might have greater potential for hazard should not be subject to control."[570]

In fact, the Committee repeatedly expressed its concern that medical devices such as heart valves, cardiac pacemakers and other devices whose "failure could be life-threatening or associated with serious morbidity" were not regulated by the Medicines Act.[571] This concern has been justified and safety problems have been

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[569]Minister of Agriculture, Fisheries and Food and the Minister of Health (1967) p5.
[570]Medicines Commission et al (1983).
[571]Medicines Commission et al (1988) p51.

reported with the Edwards-Duromedics bileaflet heart valve[572] and the Bjork-Shiley convexo-concave heart valve.[573]

On 1 January 1993, Directive 90/385/EEC relating to active implantable medical devices was implemented into UK legislation by The Active Implantable Medical Devices Regulations 1992.[574] These regulations introduced "essential requirements" for devices, requirements for clinical investigations, and the CE marking system to denote that the device satisfies the regulations and enforcement provisions. An "active implantable medical device" is defined as:

> " an instrument, apparatus, appliance, material or other article, whether used alone or in combination, together with any accessories or software necessary for its proper functioning, which -
>
> (a) is intended by the manufacturer to be used for human beings-
>
> (i) in the diagnosis, prevention, monitoring, treatment or alleviation of disease or injury,
>
> (ii) in the investigation, replacement or modification of the anatomy or of a physiological process, or
>
> (iii) in control of conception;
>
> (b) does not achieve its principal intended action by pharmacological, chemical, immunological or metabolic means;
>
> (c) relies for its functioning on a source of electrical energy or a source of power other than that generated directly by the human body or by gravity; and
>
> (d) is intended to be totally or partially introduced into the human body (whether surgically or medically, including being introduced into a natural orifice) and which is intended to remain in the human body after

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[572]Dyer (1989).
[573]CSM (1990d).
[574]S.I. 1992/3146. Amended by S.I. 1995/1671.

completion of the surgical or medical procedure during which it is introduced;

even if it is intended to administer a medicinal product as defined in the Medicines Act 1968 or incorporates as an integral part a substance which, if used separately, would be a medicinal product as so defined." [575]

This definition includes heart pacemakers, implantable drug infusion pumps, implantable neuromuscular stimulators, cochlear implants and implantable defibrillators.[576]

On 21 December 1994, Directive 93/42/EEC relating to medical devices was implemented by The Medical Devices Regulations 1994.[577] These regulations introduced a scheme for classification of devices according to risk, CE marking system, essential requirements for devices and enforcement provisions. A "medical device" is defined as

" an instrument, apparatus, appliance, material or other article, whether used alone or in combination, together with any software necessary for its proper application, which -

(a) is intended by the manufacturer to be used for human beings for the purpose of -

(i) diagnosis, prevention, monitoring, treatment or alleviation of disease,

(ii) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,

(iii) investigation, replacement or modification of the anatomy or of a physiological process, or

(iv) control of conception; and

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[575]Regulation 2(1).
[576]MDD (1993g).
[577]S.I. No. 3017. The transitional period relating to these regulations ends on 13 June 1998.

(b) does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, even if it is assisted in its function by such means,

even if it is intended to administer a medicinal product as defined in Council Directive 65/65/EEC or incorporates as an integral part a substance which, if used separately, would be a medicinal product as so defined and which is liable to act upon the body with action ancillary to that of the device."[578]

This definition includes: absorbable surgical materials (including sutures and bone cements); intra-uterine contraceptive devices; contact lens care products; some wound dressings and dental products; hip prostheses; syringes; operating theatre equipment; tongue depressors; walking frames; and CT scanners.[579]

The MCA explained that some products which were controlled under the Medicines Act 1968 as "medicinal products" would now be controlled by these new regulations. The categories of products transferred included: absorbable surgical materials (including sutures and bone cements), intra-uterine contraceptive devices; contact lens care products, some wound dressings and dental products.[580]

There are a three types of borderline products which incorporate or administer medicinal products:

- Devices which are used to administer medicinal products (e.g. a syringe marketed empty) *[considered to be a medical device];*
- Devices for administration of medicinal products such that the device and the medicinal product form a single integral product designed to be used exclusively in the given combination and which is not reusable (e.g. a syringe marketed pre-filled) *[considered to be a relevant medicinal product];* and

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[578]Regulation 2(1).
[579]MLX 210 and MDD (1993g).
[580]MLX 210.

- Devices incorporating as an integral part a substance which, if used separately, may be considered to be a medicinal product and which is such that the substance is liable to act upon the body with action ancillary to that of the device (e.g. a heparin coated catheter) *[considered to be a medical device]* [581]

A third Directive relating to *in-vitro* diagnostic medical devices has been proposed and was due to come into effect in 1997, but it has not been issued yet.[582] An "*in-vitro* medical device" is defined as:

> " any medical device which is a reagent, reagent product, kit, instrument, apparatus or system whether used alone or in combination, intended by the manufacturer to be used *in vitro* solely or principally for the examination of substances derived from the human body for the purpose of providing information relevant to the detection, diagnosis, monitoring or treatment of physiological states, states of health or disease or congenital abnormality." [583]

This definition would include blood grouping reagents, pregnancy testing kits and hepatitis B test kits.[584]

The former system of voluntary regulation of medical devices was administered by the Medical Devices Directorate of the Department of Health. The Medical Devices Agency (MDA) is now responsible for the control of medical devices.[585] The MDA states that its primary task is:

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[581]MDD (1995).
[582]Draft Council Directive III/D/4041/92-EN.
[583]MDA (1994b).
[584]MDA (1993d).
[585] The MDA listed the medical devices which it regulates as including:

> " Aids for disabled people; anaesthetic machines and monitors; apnoea monitors; artificial limbs; artificial eyes; blood transfusion and filtration devices; breast implants; cardiac monitors; cardiopulmonary bypass devices; clinical thermometers; condoms; contact lenses and prescribable spectacles; CT scanners; defibrillators; dental equipment and dentures; dental material and restoratives; diagnostic X-ray equipment; dialysers; dressings and wound healing devices; electrosurgery devices; endoscopes; enteral and parenteral feeding systems; examination gloves; fetal monitors; hearing aids and inserts; heart valves; hospital beds; hydrocephalus shunts; incontinence pads; infant incubators and warmers; infusion pumps and controllers; intra-uterine devices; intravascular catheters and cannulae; laboratory equipment; lithotripters; medical textiles, hosiery and surgical supports; medical lasers; operating tables; orthopaedic implants; ostomy and incontinence appliances; pacemakers; physiotherapy equipment; prescribable footwear; pressure sore relief devices; radiotherapy machines; resuscitators; scalpels; special support seating; sphygmomanometers; suction devices; surgical

> " To help safeguard public health by working with users, manufacturers and legislators to ensure that medical devices meet appropriate standards of safety, quality and performance and that they comply with relevant Directives of the European Union." [586]

The functions of the MDA are to: audit the quality assurance systems of medical device manufacturers supplying the UK market and publish a register of approved companies; investigate adverse incidents associated with medical devices; manage an on-going programme to evaluate medical devices and publish reports; offer advice to Ministers, the Department of Health, the National Health Service and other healthcare providers, manufacturers and other customers; provide advice on the Directives; and assess applications from manufacturers for clinical investigations with new devices.[587] In its annual reports, the MDA has reported the "highlights" of its activities and these are listed in Appendix XX.

In relation to reports of adverse incidents to medical devices, the MDA issues the following types of response:

- **Device Bulletins** are documents which contain guidance and information of a more general management interest. They are written as a result of experience gained from adverse incident investigation combined with our contacts with manufacturers and users, our device evaluations and other sources of information.
- **Hazard Notices** are issued in situations where there is a potential for death, serious injury or illness related to the use of a medical device. The full text of each Hazard Notice is sent to those organisations in the NHS and independent sector where action is required to be taken. Any member of the public requiring information on a particular notice is advised to contact their General Practitioner.

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instruments and gloves; sutures, clips and staples; syringes and needles; therapeutic x-ray equipment; ultrasound imagers; urinary catheters, vaginal speculae and drainage bags; ventilators; walking aids; and wheelchairs."
Taken from MDA's internet page (mda_mail@mda.win-uk.net).

[586] Ibid.

[587] Ibid.

- **Safety Notices** are used to recommend or inform the following:

  - where it is possible to improve safety by long term actions;

  - where it is necessary to repeat warnings on long standing problems;

  - to follow up manufacturers' field modifications.[588]

Appendix XIX lists all device bulletins, Hazard Notices and Safety Notices issued by the MDA in the period 1995 to 1997.

The regulation of medical devices has always been a controversial issue because these devices were not fully integrated into the Medicines Act, and the few products which were integrated are not now "relevant medicinal products", in terms of the 1994 Regulations. There have been several high profile claims for compensation involving adverse reactions which occurred with medical devices, such as Bjork Shiley heart valves, silicone breast implants and the Dalkon Shield intrauterine contraceptive device.[589] The new regulations relating to medical devices are a definite improvement but, as with the homeopathic registration scheme, it remains to be seen how effective the regulatory scheme will be over the coming years. However, the Author suggests that initial impressions are that the MDA is operating very efficiently.

4.6 Conflict of Interest

It has been alleged by the National Consumer Council in their report, "Balancing Acts - Conflicts of Interest in the Regulation of Medicines", that a number of conflicts of interest exist in relation to medicinal products:

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[588] Information taken from the MDA's web site.
[589] For example, Dyer (1990a).

" • within the Department of Health - as both the promoter of the competitiveness of the pharmaceutical industry, and the department charged with public health and safety;

• within expert licensing and drug regulatory committees - where (with the exception of Committee chairmen) expertise is recognised by appointment to such important Committees on the one hand, and rewarded by consultancy contracts on the other;

• between those who wish to provide optimal health care services, and those responsible for cutting the growth of drug budgets;

• between 'expert' and 'consumer' voices on regulatory committees - where the need for an impartial lay voice may sometimes conflict with the need to train and inform in order to contribute effectively to committee work;

• within the Medicines Control Agency - ensuring the provision of safe medicines on one hand, and providing a quality service to their sole funders (the industry) on the other;

• within the industry - the need to give clear and unambiguous information about medicines is offset by a fear of giving competitors helpful information about new drugs;

• between prescribers, who wish to 'make their patients better', and their patients who want to know fuller details of the potential side effects of medicines;

• among community pharmacists - where the value as independent, expert sources of information on medicines is threatened by the intensity of advertising and sales promotions directed towards them (as retailers of pharmaceutical companies and their sales representatives)." [590]

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[590]NCC (1993) pp2-4.

The National Consumer Council further stated:

> " Some of these conflicts are unlikely ever to be resolved. Experts will continue to be sought for the breadth of their knowledge, and grants will continue to be given for scientific knowledge. But where such conflicts persist, clear and transparent safeguards need to be built into the system to boost and encourage consumer confidence. This will be particularly important when mutual recognition of drug licensing comes into force under EC regulations." [591]

In relation to potential conflicts of interest, the new licensing system has made various provisions. Article 54 of Regulation 2309/93 specifies that the membership of the Committees will be made public and the professional qualifications of each member given. This Article further states that members of the Management Board, Committee Members, rapporteurs and experts should not have financial or other interests in the pharmaceutical industry which could affect their impartiality. All indirect interests which could relate to this industry should be entered in a register held by the Agency which the public may consult. Article 64 allows the participation of observers with interests in the harmonisation of regulations relating to medicinal products. Article 65 states:

> " The Management Board shall, in agreement with the Commission, develop appropriate contacts between the Agency and the representatives of the industry, consumers and patients and the health professions."

The allegations concerning conflict of interest in relation to the expert advisory Committees are of particular concern. In 1987, the Code of Practice requiring Members of the Medicines Commission and of the other expert Committees to declare their interests in the pharmaceutical industry was revised. For the first time, these interests were made public and were published in the Annual Reports of the

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[591] Ibid.

Commission and of the Committees. The new Code, "Declaration of Interests: A Code of Conduct for Members of the Medicines Commission and Section 4 Committees and Sub-Committees", set out the reason for this decision:

> " The advice of the Commission and the Committees concerns matters which are connected with the pharmaceutical industry and it is therefore desirable that members should have a good understanding of the work of the industry. It is also desirable that some members should have practical experience of the scientific problems of product development. The pharmaceutical industry relies heavily on the advice of doctors and pharmacists outside the industry in, for example, the universities. To avoid any public concern that commercial interests might affect the advice of the Commission and the Committees, Ministers have decided that the arrangements which govern relationships between members and the pharmaceutical industry and information on significant and relevant interests should be on public record." [592]

The Code currently applies to the Medicines Commission, all the section 4 Committees and their Sub-Committees, except for the British Pharmacopoeia Commission.[593] No explanation is given in the Code for this exclusion. However, this exclusion could be connected to the fact that commercial interests are not so affected by the work of the Pharmacopoeia, that industrial scientists are members of the Commission and the Commission liaises with the pharmaceutical industry on many issues.

The Code identifies two different types of interest in the pharmaceutical industry,[594] which require to be declared: "personal interests" and "non-personal interests". A "personal interest" involves:

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[592]Medicines Commission et al (1994) p.63.
[593]Initially Veterinary Products Committee members were also excluded from declaring their interests.
[594] The Code defines "pharmaceutical industry" as including:
"a. companies, partnerships or individuals who are involved with the manufacture, sale or supply of medicinal products subject to the licensing provisions in the Medicines Act;

" Payment to the member personally. The main examples are:

1. Consultancies: any consultancy, directorship, position in or work for the pharmaceutical industry which attracts regular or occasional payments in cash or kind.
2. Fee-paid work: any work commissioned by the pharmaceutical industry for which the member is paid in cash or kind.
3. Shareholdings: any shareholding in or other beneficial interest in shares of the pharmaceutical industry. This does not include shareholdings through unit trusts or similar arrangements where the member has no influence on financial management."[595]

A "non-personal interest" involves:

" Payment which benefits a department for which a member is responsible, but is not received by the member personally. The main examples are:

1. Fellowships: the holding of a fellowship endowed by the pharmaceutical industry.
2. Support by the pharmaceutical industry: any payment, other support or sponsorship by the pharmaceutical industry which does not convey any pecuniary or material benefit to a member personally but which does benefit his/her position or department. For example,
   i. a grant from a company for the running of a unit or department for which a member is responsible.
   ii. a grant or fellowship or other payment to sponsor a post or a member of staff in the unit for which a member is responsible. This does not include financial assistance for students.

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b. trade associations representing companies involved with such products;
c. companies, partnerships or individuals who are directly concerned with research, development or marketing of a medicinal product which is being considered by the Commission or one of the Committees or Sub-Committees." Medicines Commission et al (1994) p64

[595]Ibid p65.

iii. the commissioning of research or other work by, or advice from, staff who work in a unit for which the member is responsible."[596]

When the members of the Commission, the Committees and the Sub-Committees are appointed, they are required to inform the Department of Health, in writing, of their current personal and non-personal interests. It is considered inappropriate for the chairman of the Medicines Commission and of the Section 4 committees to have any current personal interests in the pharmaceutical industry. At meetings before any application or data pertaining to a product is discussed, members must make a full declaration of all their relevant interests and state whether they are personal or non-personal and whether they are specific or non-specific to the product under consideration. The Code sets out detailed guidance:

" a. A member must declare a personal specific interest if he or she has at any time worked on the product under consideration and has personally received payment for that work, in any form, from the pharmaceutical industry. The member shall take no part in the proceedings as they relate to the product, except at the Chairman's discretion to answer questions from members. If the interest is no longer current, the member may declare it as a lapsed personal specific interest.

b. A member must declare a personal non-specific interest if he or she has a current interest in the pharmaceutical company concerned which does not relate specifically to the product under discussion. The member shall take no part in the proceedings as they relate to the product, except, at the Chairman's discretion, to answer questions from other members.

c. A member must declare a non-personal specific interest if he or she is aware that the department for which he or she is responsible has at any time worked on the product but the member has not personally received payment, in any form, from the pharmaceutical industry for the work done. The member may

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[596]Ibid p65-66.

take part in the proceedings unless he or she has personal knowledge of the product through his or her own work or through direct supervision of other people's work, in which case he or she should declare this and not take part in the proceedings (except to answer questions).

d. A member must declare a non-personal non-specific interest if he or she is aware that the department for which he or she is responsible is currently receiving payment from the pharmaceutical company concerned which does not relate specifically to the product under discussion. The member may take part in the proceedings unless, exceptionally, the Chairman rules otherwise."

[597]

In addition, a member must declare a current personal interest if it is in a company which markets a rival to the product under consideration. If in doubt, members are encouraged to consult their chairman to determine whether an interest should be declared.

Appendix XXI lists the personal and non-personal interests declared by the current members of the Medicines Commission and the CSM.

In its report, "Balancing Acts - Conflicts of Interest in the Regulation of Medicines", the National Consumer Council (NCC) recognised that it would be "almost impossible" to disbar non-personal interests, but expressed the view that members of the various expert committees should not have personal interests, particularly consultancy contracts, in the pharmaceutical industry.[598] It is agreed that the independence and impartiality of committees is of crucial importance. But is there evidence of a conflict of interest within the UK system of expert committees?

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[597]Ibid p67-68.
[598]NCC (1993) p13-14.

Dame Rosalinde Hurley, former chairman of the Medicines Commission, wrote a letter to The Lancet in response to the NCC report in which she pointed out that section 2(3) of the Medicines Act requires that the pharmaceutical industry is represented on the Medicines Commission.[599] The NCC quoted examples of problems arising from conflicts of interests in Italy, the United States and Portugal; no example is given of any reported problems within the UK. The Report mentioned that the number of pharmaceutical companies mentioned in the personal interests of members of the Medicines Commission and Committee on Safety of Medicines increased between 1990 and 1992. In respect of the Medicines Commission, the Report stated that the increase in named companies was from 26 to 34, and for the CSM, the increase was from 14 to 35. However, the Author disagrees with the calculation of these figures and it is apparent from Table 27 that the combined total of personal interests in the pharmaceutical industry has not changed by much since 1987. It could be argued that a greater spread of companies represented, where the combined total of personal interests remains about the same, is "better" than having fewer companies with greater representation. However, in 1997, the number of members of the CSM increased by 8 members and there was an increase in the number of personal interests up to a total of 62.

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[599]Hurley (1994). The membership of the Commission has been discussed in more detail in Chapter 3.

Table 27 Analysis of the Total Declared Interests of the Members of the Medicines Commission and the CSM (1987 - 1996)

MEDICINES COMMISSION			
Year	*No. of Members*	*Combined Total of Personal Interests*	*No. of Companies Represented*
1987	25	17 members with 50 interests; 8 members with no interests	31
1988	24	17 members with 41 interests; 7 members with no interests	23
1989	24	15 members with 43 interests; 9 members with no interests	25
1990	24	15 members with 41 interests; 9 members with no interests	28
1991	22	13 members with 37 interests; 9 members with no interests	29
1992	21	14 members with 42 interests; 7 members with no interests	35
1993	20	12 members with 44 interests; 8 members with no interests	36
1994	20	12 members with 45 interests; 8 members with no interests	36
1995	20	12 members with 39 interests; 8 members with no interests	34
1996	19	11 members with 48 interests; 8 members with no interests	41

Table 27 contd.

COMMITTEE ON SAFETY OF MEDICINES			
1987	20	12 members with 34 interests; 8 members with no interests	27
1988	21	14 members with 42 interests; 7 members with no interests	36
1989	21	13 members with 37 interests; 8 members with no interests	31
1990	21	12 members with 39 interests; 9 members with no interests	34
1991	21	12 members with 48 interests; 9 members with no interests	37
1992	21	12 members with 44 interests; 9 members with no interests	36
1993	22	15 members with 31 interests; 7 members with no interests	27
1994	21	10 members with 27 interests; 11 members with no interests	25
1995	21	12 members with 29 interests; 9 members with no interests	24
1996	29	18 members with 62 interests; 11 members with no interests	44

The NCC also stated that independent members and members of consumer groups are not appointed to expert committees. In relation to independent members, this is clearly untrue as every committee has members without personal interests or non-personal interests, and the Medicines Commission always has a lawyer as one of its members.[600] Perhaps there could be representation of consumers on the Medicines Commission; this would be of more benefit than appointing consumer representatives to the Section 4 Committees (which deal with technical material) as the Medicines Commission is responsible for making policy decisions and oversees the work of the other Committees.

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[600]The current legal representative is Dr Christopher Newdick.

The NCC has also suggested that there should be a review of the system for appointing Committee members. Ultimately, the appointment of Committee members is determined by the Health and Agriculture Ministers. However, the Ministers are required by section 2(2) of the Medicines Act to consult with "such organisations as they consider appropriate"; Ministers also act on the advice of the Medicines Commission. The involvement of the NCC in this procedure is unclear.

It is inevitable that well-respected academics who are Committee members will be offered consultancies by the pharmaceutical industry. It is argued by the Author that participation in the commercial research and development of medicinal products is not necessarily detrimental to the process of licensing medicinal products as the Committee members with commercial interests will have insight into current industry practices. It is further argued that the existence of these interests does not mean that the CSM is not able to make impartial decisions.

What may be of future concern relating to the issue of conflict of interest, however, is if there are further decisions similar to the recommendation by the Medicines Control Agency (MCA) to the Licensing Authority, to revoke the product licences for triazolam (Halcion) and by doing so, ignore the advice of two expert committees. Inman expressed concern in 1993 that there could be potential problems if a secretariat, such as the MCA, was "expected to serve a scientifically independent committee on the one hand and the Minister of the day on the other".[601]

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[601]Drug Safety Research Unit (1993) p30.

4.7 Changes in the Legal Status of Medicinal Products

Article 1 of Directive 92/26/EEC sets out provisions relating to the classification of medicinal products for human use in the Community into:

" - medicinal products subject to medical prescription;

- medicinal products not subject to medical prescription."

A "medical prescription" is defined as:

"any prescription issued by a professional person qualified to prescribe medicinal products."[602]

Article 2 states that, after a marketing authorization has been granted, the competent authorities shall specify the classification of the medicinal product into one of these categories. Article 3 provides that medicinal products will be subject to medical prescription where they:

" - are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision, or

- are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health, or

- contain substances or preparations thereof the activity and/or side effects of which require further investigation, or

- are normally prescribed by a doctor to be administered parenterally."

Part III of the Medicines Act 1968 sets out various provisions relating to the sale or supply of medicinal products. This part of the Act has been amended by the 1994 Regulations to cover marketing authorisations. "Medicines, Ethics and Practice" published by the Royal Pharmaceutical Society of Great Britain contains an excellent

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[602] Article 1(2).

summary of the provisions of Part III. There are three classifications of medicinal products:

1. General Sale List medicines (GSL)

   Those medicinal products which in the opinion of the appropriate Ministers can, with reasonable safety, be sold or supplied otherwise than by or under the supervision of a pharmacist are known as general sale list (GSL) medicines and are listed in the general sale list Order.

2. Prescription Only Medicines (POM)

   Other medicinal products which may be sold or supplied only from pharmacies in accordance with a prescription given by a practitioner are specified in the prescription-only Order.

3. Pharmacy Medicines (P)

   Any medicinal product which is not a prescription-only medicine or a general sale list medicine is a pharmacy medicine.[603]

There have been more statutory instruments relating to the sale or supply and classification of medicinal products than any other aspect of the Medicines Act. It is possible for medicinal products to be designated a legal status, which is later changed by statutory instrument. This "switching" has become a controversial issue because increasing numbers of prescription only medicinal products are now being reclassified as "pharmacy medicines" (i.e. available without a prescription but sold or supplied under the supervision of a registered pharmacist.).[604] Barber suggested that:

" Economic and philosophical considerations underlie these moves. Economic considerations include an escalating growth in spending on health care, which includes a drug bill, growing at around 12% every year. One solution is to shift more of the financial burden to individuals by encouraging them to treat themselves with non-prescription drugs. What is more, the current controls on drug spending have constrained profits in the drug industry, so more companies

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[603] Royal Pharmaceutical Society (1997) p3.

> are moving into the over the counter market. The government's philosophy on health care is that individuals should take greater responsibility for their health; trends towards less medical paternalism and more consumerism favour greater freedom to choose self treatment for palliation and cure." [605]

The economic and philosophical considerations mentioned by Barber may underlie these switches in legal status. However, the pricing structure relating to medicinal products falls outwith the scope of this thesis. It is suggested by the Author that these switches may have been made on the basis of convenience to the consumer and the fact that the products which have been "switched" have demonstrated that they are "safer" than other treatments.

Appendix XXII lists the active substances which have been "switched" in the period 1983 to 1996 from being prescription only medicines to being pharmacy medicines. However, what must be noted is that these "switches" apply to particular formulations of the active substance for use in limited circumstance and with defined dosages, and do not mean that all products containing the active substance have had their legal status amended. Also, changes in legal status have been implemented by reference not to the active substance but to the brand name of the medicinal product in question. [606].

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[604]MCA (1992j).
[605]Barber (1993).
[606] The following products have switched status in this manner:
Adcortyl in Orabase for Mouth Ulcers; Anhydrol Forte; Anusol Plus HC Ointment; Anusol Plus HC Suppositories; Beechams Hydrocortisone Cream; Boots Hydrocortisone Cream; Calacort Cream; Canesten Hydrocortisone Cream; Corlan Pellets; Cortaid Cream and Ointment; Corteze Cream; Cortiderm; Cortril Topical Ointment 1%; Daniels Hydrocortisone Cream 1%; Dioderm Hydrocortisone Cream; Efcortelan Eczema Cream; Efcortelan Eczema Ointment; Eurax HC Cream; Evacort Cream; HC Hydrocortisone Cream; Hepated Cold Sore Cream; Jungle Formula Bite and Sting Relief Cream; Lanacort Cream and Ointment; Leo Hydrocortisone Acetate Cream (0.5%) and (1%); Nicorette Plus; Perinal Spray; Pharmacort Cream (0.5%); Protocream HC; Soothelip Cold Sore Cream; Timocort Hydrocortisone Cream; Zaclovir Cold Sore Cream; and, Zovirax Cold Sore Cream. S.I. 1987/674, 1987/1250, 1993/1890, 1993/3256, 1994/3016, 1995/1384, 1996/1514 and 1996/3193.

In 1997, The Prescription Only Medicines (Human Use) Order was implemented.[607] This consolidates all the statutory instruments which have amended the status of medicinal products. The information on the status of medicinal products is now presented in a much clearer format and is not dissipated through multiple statutory instruments.

In 1997, the MCA published a Medicines Act Leaflet (MAL 77) entitled "Changing the Legal Classification in the UK of a Prescription Only Medicine for Human Use."[608] This explained that the MCA assess applications for a change in legal status in consultation with the CSM. If the CSM recommends that the product should be re-classified, then an MLX consultation letter is issued and ultimately the status of the medicinal product is changed by statutory instrument. In considering, whether the status of a medicinal product should be changed, the MCA has stated that the following issues should be considered: direct danger, indirect danger, possibility of self-diagnosis without medical supervision, risk of misuse, limited experience with the product and information to be provided to the patient.[609] Despite these stringent controls, terfenadine has been transferred back to having prescription only status because of the risk of cardiac arrhythmias.[610]

Not only have changes been made in the legal status of medicinal products from prescription only to pharmacy status, but there have also been a number of changes from pharmacy to general sale list status.[611] However, the transfer of a medicinal product from Pharmacy to General Sale List status has been described as a "far, far

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[607] S.I. 1997/1830.
[608] MCA (1997k).
[609] Ibid.
[610] CSM (1997a) and S.I. No. 1997/2044.
[611] For example, S.I. Nos. 1984/769, 1985/1540. 1987/910, 1989/969, 1990/1129, 1992/1535, 1994/2410, 1995/3216, 1980/1924, 1982/27, 1980/1927, 1980/28, 1990/1124, 1992/2938, 1994/2411, 1995/3215, 1997/1831, 1997/2043 and 1997/2045. See also "Changing the Legal Classification in the UK of a Medicine for Human Use from Pharmacy to General Sale List" - MCA (1996e).

greater step" than the transfer in status from prescription only to pharmacy.[612] Professor Florence commented:

> " Recent decisions in the United Kingdom to transfer ibuprofen and clotrimazole from pharmacy only (P) status to general sale list (GSL) status, have provoked adverse responses from the pharmaceutical profession. While these may be dismissed as expressions of self-interest, this would be to denigrate the long-established involvement of the pharmacist in the provision both of medicines and advice on medicines. The sources of these concerns should be examined for their legitimacy and the consequences of change to the legal status of medicines examined for their effect on the current means of their distribution. In having a GSL category, the UK is more liberal than most other European countries, in several of which there is a monopoly of distribution of medicines through pharmacies. [...][613]

There has been recent controversy over the decision to restrict the pack size of products containing paracetamol and aspirin, available on the general sale list by September 1998.[614] In relation to this and the situation regarding terfenadine, it was stated in an editorial in the Pharmaceutical Journal that:

> " "Terfenadine is safe when it is taken as recommended, says the Minister for Health - but from the middle of next month, the many thousands of hay fever sufferers who benefit from safely taking over-the-counter terfenadine will have to obtain prescriptions (at a cost to the National Health Service) or change to alternative products that may be more expensive but no more effective. Analgesics are safe and effective when used at the recommended doses, says the Minister of Health - but from September next year, the millions of people who use over-the-counter paracetamol or aspirin safely and effectively will have to

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[612] Pharm J (1995e).
[613] Florence (1996).
[614] Pharm J (1997h).

> pay more to do so, because smaller pack sizes are to be required by law and they cannot be produced without an increase in the price per dose.
> While we share the Minister's concern about terfenadine and paracetamol, we are not convinced that his action is entirely appropriate. Can it be right to penalise the vast majority of people who use their medicines responsibly?" [615]

Following the many changes in legal status from prescription only to pharmacy status, from 1 January 1995, the Royal Pharmaceutical Society of Great Britain required that:

> " there should be a written protocol in each pharmacy covering the procedure to be followed in that pharmacy when a medicine is supplied or advice on treatment of a medical condition is sought." [616]

However, the Consumer's Association,[617] the Radio 4 programme "You and Yours", ITN's "News at Ten"[618] and the BBC television programme "Watchdog"[619] have criticised the way in which these pharmacy protocols are operating. Li Wan Po analysed the report from the Consumers' Association and concluded that, despite flaws in the manner in which the study was conducted:

> " The latest report on our performance arouses unease. We should perhaps be thankful to the Consumers' Association for highlighting some deficiencies in our practice. By so doing, it helps us to focus on what needs to be attended to most urgently. The New Age begins now?" [620]

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[615] Ibid.
[616] Pharm J (1994). The Royal Pharmaceutical Society also provided that, by 1 July 1996, each member of staff involved in the sale of medicinal products should have completed (or be undertaking) the Medicines Counter Assistant course.
[617] Pharm J (1996a).
[618] Pharm J (1994b).
[619] Pharm J (1995b).
[620] Li Wan Po (1996) p59.

Section 67 of the Medicines Act created an offence relating to the supervision of sale or supply of pharmacy medicine.[621] Appendix XXIII lists the pharmacists who have been prosecuted for not having supervised the sale of pharmacy medicines appropriately together with the disciplinary action taken by the Statutory Committee of the Royal Pharmaceutical Society.

Appelbe and Harrison conducted a detailed study of the work of the Statutory Committee.[622] In relation to the cases involving lack of supervision, they commented:

> " It has been argued that supervision of the sale of medicines is of prime importance to the profession and, indeed, the provision has been enshrined in legislation since 1968. The Committee has also stressed that professional supervision is paramount, but, in spite of that, the sanctions applied have not been draconian." [623]

In conclusion, they stated:

> " What benefit is there to the public of the present legislative provisions, which stem from 19th century philosophy controlling the sale of such poisonous substances as strychnine and sodium cyanide. The Committee, while stressing that professional supervision is paramount, has rarely considered that failure to supervise warranted the erasure of a pharmacist's name from the register. However, as a sign of pharmacist control of the activities within a pharmacy, supervision is an important concept for the profession. The whole question of supervision needs to be considered in terms of 20th century philosophy concerned with the distribution of medicinal products from pharmacies." [624]

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[621] Section 52 of the Medicines Act 1968 sets out the provivions relating to the sale or supply of medicinal products not on the general sale list (ie. pharmacy medicines) and specifies that such products must be sold or supplied under the supervision of a pharmacist. Section 67 states that anyone who contravenes this section will be guilty of an offence.

[622] Appelbe and Harrison (1993a), (1993b), (1994a), (1994b), (1994c) and (1994d).

[623] Ibid (1993b) p565.

[624] Ibid.

In relation to changes in the legal status of medicinal products, consumers should be given as much choice as possible, however, safety is paramount. Barber has stated:

> " Overall, the shift from prescription only to pharmacy only medicines should be welcomed as it gives greater freedom of choice to patients and allows them to treat symptoms quickly. But there are risks that patients may delay consulting about serious conditions and that an unacceptably high incidence of adverse effects may result from the way that the general population uses the drug. In this risk-benefit equation only the benefits are clear; the risks, and the burden of harm that may accrue, are hard to predict." [625]

To protect consumers against these risks, it is suggested that not only should there be stronger sanctions against pharmacists who do not supervise the sale of medicinal products as this supervision protects consumers, but there should be better information for consumers about medicinal products, so as they can make informed decisions about the medicinal products they purchase. In addition, community pharmacists should be allowed to monitor the safety of the medicinal products they dispense and report any adverse reactions via the Yellow Card Scheme; both of these latter issues are discussed later in this chapter.[626]

4.8 Information Supplied to Patients

4.8.1 Patient Information Leaflets

Information relating to medicinal products is available from doctors, pharmacists, patient information leaflets, other consumers and the media. Unfortunately, the

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[625]Ibid.
[626]Sections 4.8 and 4.10.

development of the concept of "trial by television", as discussed in Chapter One,[627] has meant that patients are not necessarily being given accurate and impartial information about medicinal products because of the sensationalised manner in which information about these products is presented. The most detailed advice which a patient will receive about a medicinal product will originate from a patient information leaflet. However, the ABPI has commented:

> " Information to patients about their medicines expressed in terms which they can both understand and retain, is tremendously important. Anything which the industry does, however, should not usurp the role of the prescriber and the pharmacist."[628]

Detailed provisions relating to patient information leaflets were introduced by Directive 92/27/EEC, which was implemented in full by the 1994 Regulations and in part by S.I. No. 1992/3274. From 1 January 1994, all pharmaceutical companies were required to include a patient information leaflet in all packs of newly licensed medicinal products and medicinal products, which were subject to licence renewal. By the end of 1998, all packs of medicinal products will contain patient information leaflets.[629] Prior to these regulations coming into force, pharmaceutical companies had provided leaflets on a voluntary basis.[630]

The preamble to Directive 92/27/EEC explains that this Directive supplements the provisions on labelling in Directive 65/65/EEC and the provisions on package leaflets in 75/319/EEC, and brings them together in a single text.

Article 1 states that this Directive applies to "relevant medicinal products" and defines the various terms used: "name of the medicinal product", "common name", "strength of the medicinal product", "immediate packaging", "outer packaging",

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[627]p10.
[628]ABPI (1995b).
[629]Ibid.

"labelling", "package leaflet" and "manufacturer". Article 2 of this Directive sets out the "particulars" which should appear on the outer packaging of a medicinal product and include: the name of the medicinal product, a statement of the active ingredients, the pharmaceutical form and contents by weight, a list of excipients, the route of administration, any warnings, expiry date, any storage precautions, batch number, instructions and name, address and number of marketing authorization holder. Where there is no outer packaging the same information should appear on the immediate packaging.

Article 4 specifies that these "particulars" must be "easily legible, clearly comprehensible and indelible". Article 6 specifies that a package leaflet is obligatory unless all the information required by Article 7 has been directly conveyed on the outer or immediate packaging. Article 7 states that the package leaflet must be drawn up in accordance with the summary of product characteristics and include: information for the identification of the medicinal product (name, pharmaceutical form, pharmaco-therapeutic group and details of marketing authorization holder); the therapeutic indications; a list of information which is necessary before taking the medicinal product, such as contra-indications, appropriate precautions for use, forms of interaction with other medicinal products and other forms of interaction (for example, alcohol, tobacco, foodstuffs) which may affect the action of the medicinal product, and special warnings (use by children, elderly and pregnant women); the necessary and usual instructions for proper use (including duration of treatment and action to be taken in the event of overdose); and a description of the undesirable effects which can occur under normal use of the medicinal product.

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[630] Ibid. In 1988, the ABPI published guidance on the drafting of patient information leaflets.

The MCA summarised examples of reasons given by pharmaceutical companies, as to why certain information should be excluded from patient information leaflets:

" a concern that a patient would be scared by the leaflet and not take the drug. The language used should be sensitive to the possibility that patients may react to the information given by not taking the drug, but patients should be provided with information that enables them to use the product safely in conjunction with any information given by the doctor or pharmacist.

b. concern that the doctor-patient relationship might be harmed. The language used should be sensitive to the need to avoid upsetting the doctor-patient relationship, but this is not a reason for omitting information.

c. considering that the information would not relate to the patient. If the contraindication, warning or side-effect is in the licence, it should be mentioned in the leaflet.

d. suggesting that certain warnings in the product information were for the doctor, and the patient did not need to know them. This is contrary to the spirit and requirement of the EC Directive. It is not normally justifiable to provide certain information to a doctor , but conceal it from a patient. This leaflet is to inform the patient, not the doctor. All contra-indications, precautions, warnings and adverse reactions should be included specifically or covered by appropriate references.

e. responsibility for safe drug use lies with the doctor, and that leaflets should contain minimal information and "roll-up" warnings. This view is not compatible with free access to information enabling patients to take more responsibility for their own health and determine the way they wish to be treated. Also it does not take account of doctors' limited time for consultation and explanation and an increasing availability of products without prescription. Information must be comprehensive. Nevertheless, leaflet information should not compromise patient safety." [631]

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[631]MCA (1993) pp14-15.

However, it is the opinion of the Author that the benefits of giving patients information about the medicinal products they ingest outweighs any disadvantages. Many authors have acknowledged that patients should be given information about medicinal products.[632] For example, Gibbs et al conclude:

> " that patients welcome the idea of receiving PILs. [patient information leaflets] They improve patients' knowledge of how to take their medicines correctly and their awareness of potential side effects. Importantly, patients who receive leaflets are more satisfied than those who do not. These overall benefits justify the use of leaflets on a routine basis."[633]

The ABPI has published a compendium of patient information leaflets. Appendix XXIV presents a selection of these leaflets. The Author decided to compare an example of a patient information leaflet (Table 28) with its equivalent Data Sheet (Table 29), which contains the prescribing information available to doctors. The information given by Sandoz Pharmaceuticals relating to its medicinal product Clozaril was compared. The example illustrated that more information was given to the doctor but, in the opinion of the Author, the patient was given sufficient information in his leaflet to assess the risks and benefits of undergoing treatment with this medicinal product.

The National Consumer Council has commented that:

> " the patient information leaflet is the lowest in the information hierarchy. This in itself is not necessarily a problem, provided that:
> - the information is *truly* informative about the risks and benefits of the medicine; and

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[632] George (1987), BMJ (1980d), McMahon et al (1987), Hermann et al (1978), George et al (1983), Lervy and Clayton (1986), Ridout at al (1986), Gibbs et al (1989a) and (1989b), Baker (1991) and George (1992).
[633] Gibbs et al (1989) p723.

- the more detailed categories of information are available for patients who want to understand their medical condition and the range of treatment options available, in a more active and informed way."[634]

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[634] NCC (1994) pp39-40.

Table 28 Patient Information Leaflet for Clozaril

Clozaril Tablets

What you should know about Clozaril Tablets
Please read this leaflet carefully before you start to take your medicine, even if you have already been taking Clozaril for some time. If you have any questions or you are not sure about anything ask your doctor or pharmacist.

The name of your medicine is Clozaril and it contains clozapine. This medicine is used to treat the symptoms of schizophrenia.

Things to remember about Clozaril

1. Make sure it is safe for you to take this medicine. You must have a blood test before you start (see inside leaflet).
2. Remember to take your tablets exactly as your doctor tells you. Never change the dose yourself.
3. Clozaril can sometimes cause side-effects. You can find more information inside this leaflet.
4. You must have regular blood tests for as long as you are taking Clozaril.
5. If you get any kind of fever, infection or a sore throat, tell your doctor immediately.
6. Keep your medicine away from children.

You will find more about your medicine inside this leaflet.

Your medicine is called Clozaril. It contains clozapine and is used to treat the symptoms of schizophrenia.

Before taking your medicine
Before you start to take Clozaril you must have a blood test to make sure you can take it.

You must also have regular blood tests for as long as you are taking this medicine. Your doctor will tell you when and where to have the tests. They will be every week for the first few months but may reduce to every two weeks later on. You must not miss these tests. Your doctor will not be able to let you have more tablets if you do.

If the answer to any of the following questions is 'yes' tell your doctor.

1. Have you taken this medicine before, and if so, were you allergic to it or has it upset you?
2. Do you, or have you ever, suffered from any blood disorder or bone marrow disease?
3. Do you or your family have a history of fits?
4. Are you taking any other medication?
5. Are you pregnant or breast feeding?
6. Have you ever suffered from severe mental depression?
7. Have you ever had any problems with alcohol or drug abuse?
8. Do you have heart, kidney or liver problems or glaucoma?
9. Have you ever experienced difficulty in passing urine?

Clozaril is not recommended for children.

Taking your medicine
Take your medicine exactly as your doctor tells you. Your doctor will sometimes change the number of tablets you take.

The label will tell you how much medicine to take and how often. If it does not, or you are not sure, ask your doctor or pharmacist.

You must never change the dose yourself.

Remove the tablet from the foil as shown in the picture.

Always take the tablets with water and swallow them whole.

If you forget to take a dose, take another as soon as you remember, unless it is time for your next dose, then go on as before.

Overdose: If you accidentally take too many Clozaril tablets contact your doctor immediately or go to your nearest casualty department.

After taking your medicine
Clozaril may affect your blood in a way that makes it harder for you to fight any infection. This is why you must not miss your blood tests.

If you develop any sign of infection, such as an increase in temperature, or symptoms like flu or a sore throat, tell your doctor immediately.

Clozaril may make you feel drowsy, if you are affected in this way do not drive or operate machinery. Care may be necessary if you take part in activities requiring complete mental alertness.

Clozaril may increase the effects of sedatives or alcoholic drinks. Do not drink alcohol.

Clozaril may cause fits in susceptible patients.

Apart from drowsiness or tiredness the most common side-effects are a fast heart beat and making extra saliva.

At the start of treatment you may have a dry mouth or constipation and you may feel sick or put on some weight. These effects usually stop after a short time.

Clozaril may cause you to sweat more and you may feel dizzy or develop a headache or suffer blurred vision. Involuntary loss of urine or difficulty in passing urine may also occur.

Clozaril may also cause shortness of breath and a sensation of pain in the chest.

If these or any other side effects occur tell your doctor.

Clozaril sometimes makes people have tremors or feel rigid in the hands or legs. If this happens to you, tell your doctor as soon as possible.

Storing your medicine
Leave the tablets in their packing. Only remove them when it is time for your next dose.

Keep your tablets in a safe place where children cannot reach them, your medicine could harm them.

If your doctor decides to stop your treatment, return any leftover tablets to your pharmacist.

What's in your medicine
Clozaril are yellow, round tablets, they contain either 25 or 100 mg of clozapine.

Further information
REMEMBER: This medicine is only for you. Only a doctor can prescribe it for you. Never give it to anyone else.

This leaflet does not contain complete information about your medicine. If you have any questions or are unsure about anything ask your doctor or pharmacist.

Clozaril is a registered Trade Mark.

Clozaril tablets are manufactured by: Sandoz Pharmaceuticals, Calverly Lane, Horsforth, Leeds LS18 4RP for Sandoz Pharmaceuticals, Frimley Business Park, Frimley, Camberley, Surrey GU16 5SG; and Sandoz Products (Ireland) Ltd, Airton Road, Tallaght, Co. Dublin.

25 mg tablets: PL 0101/0228 PA 13/46/1
100 mg tablets: PL 0101/0229 PA 13/46/2

Table 29 Data Sheet for Clozaril

CLOZARIL®

Presentation

25 mg tablets: Yellow, flat, circular tablets with a bevelled edge, of 8.3 mm diameter and weighing approximately 95 mg, coded CLOZ 25 on one side and with a breakline on the other. Each tablet contains 25 mg clozapine.

100 mg tablets: Yellow, flat, circular tablets with a bevelled edge, of 10 mm diameter and weighing approximately 380 mg coded CLOZARIL 100 on one side and plain on the other. Each tablet contains 100 mg clozapine.

Uses

Principal action: Clozapine is an antipsychotic agent which differs from conventional neuroleptics. In animal experiments, it does not induce catalepsy or inhibit apomorphine- or amphetamine-induced stereotyped behaviour. It has weak dopamine receptor-blocking activity at both D1 and D2 receptors, but potent alpha-adrenoceptor blocking, anticholinergic, antihistaminic and arousal reaction inhibiting effects. It has also been shown to possess antiserotoninergic properties.

Clinically, Clozaril produces rapid and marked sedation, and exerts strong antipsychotic effects. In particular, the antipsychotic effects have been demonstrated in schizophrenic patients resistant to other drug treatment. In such cases, Clozaril has proven effective in relieving both positive and negative schizophrenic symptoms, with more than half of patients showing clinically relevant improvement.

Indications: Clozaril is indicated in treatment-resistant schizophrenic patients, ie patients who are non-responsive to, or intolerant of, conventional neuroleptics.

Non-responsiveness is defined as lack of satisfactory clinical improvement despite the use of adequate doses of at least two marketed neuroleptics prescribed for adequate durations.

Intolerance is defined as the impossibility to achieve adequate benefit with conventional neuroleptic drugs because of severe and untreatable neurological adverse reactions (extrapyramidal symptoms or tardive dyskinesia).

Dosage and administration Initiation of Clozaril treatment must be in hospital in-patients and is restricted to those patients with a white blood cell count >3500/mm³ and a normal differential blood count. *The use of Clozaril is restricted to patients who are registered with the Clozaril Patient Monitoring Service.*

The dosage must be adjusted individually. For each patient the lowest effective dose should be used.

Adults

Initial dose: 12.5 mg (one half of a 25 mg tablet) once or twice on the first day, followed by one or two 25 mg tablets on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 to 50 mg in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50 to 100 mg at half-weekly or, preferably, weekly intervals.

Therapeutic dose range: In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day in divided doses. The total daily dose may be divided unevenly, with the larger portion at bedtime.

Maximum dose: A few patients may require larger doses to obtain maximum therapeutic benefit. Judicious increments (not exceeding 100 mg per increment) are permissible up to a maximum dose of 900 mg/day. Adverse reactions may increase at doses over 450 mg/day, in particular seizures.

Maintenance dose: After achieving maximum therapeutic benefit, many patients can be maintained on lower doses. Careful downward titration to the level of 150 to 300 mg/day given in divided doses is recommended. At daily doses not exceeding 200 mg, a single administration in the evening may be appropriate.

Ending therapy: If termination of Clozaril therapy is planned, a gradual reduction in dose is recommended over a 1 to 2 week period. If abrupt discontinuation is necessary the patient should be carefully observed for the recurrence of psychotic symptoms.

Re-starting therapy (providing the patient has not ceased therapy due to a haematological abnormality – see Precautions): In patients in whom the interval since the last dose of Clozaril exceeds 2 days, treatment should be re-initiated with 12.5 mg (one half of a 25 mg tablet) given once or twice on the first day. If this dose is well tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment. However, if patients have previously experienced respiratory or cardiac arrest with initial dosing, and were then able to be successfully titrated to a therapeutic dose, re-titration should be done with extreme caution.

Switching from a conventional neuroleptic to Clozaril: It is generally recommended that Clozaril should not be used in combination with conventional neuroleptics, including depot preparations, which may have a myelosuppressive effect. When Clozaril treatment is to be initiated in a patient who is on oral neuroleptic therapy, it is recommended that the conventional neuroleptic be discontinued by tapering the dosage downwards, before Clozaril therapy is initiated as described above.

Children: Not recommended.

Use in the elderly: In elderly patients it is recommended to initiate treatment at a particularly low dose (12.5 mg given once on the first day) and to restrict subsequent dose increments to 25 mg/day.

Other special patient groups: Patients with a history of epilepsy should be closely monitored during Clozaril therapy since dose-related convulsions have been reported. Therefore in patients with a history of seizures, as well as those suffering from cardiovascular, renal, or hepatic disorders, the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments.

Contra-indications, warnings, etc

Contra-indications: Use in patients hypersensitive to the drug. Patients with a history of drug-induced neutropenia/agranulocytosis, or with myeloproliferative disorders, must not be treated with Clozaril.

Other contra-indications are alcoholic and toxic psychoses, drug intoxication, comatose conditions, circulatory collapse and/or CNS depression of any cause and severe hepatic, renal or cardiac failure.

Warning: Clozaril can cause agranulocytosis. A fatality rate of up to 1 in 300 has been estimated when Clozaril was used prior to recognition of the risk of agranulocytosis and the need for routine blood monitoring. Since that time careful monitoring of patients has been demonstrated to be effective in markedly reducing the risk of fatality.

Because of the risk associated with Clozaril therapy its use is limited to treatment-resistant schizophrenic patients (see 'Indications'):

1. who have normal leucocyte findings (white blood cell count and differential blood count), and
2. in whom regular leucocyte counts can be performed weekly during the first 18 weeks and at least every two weeks thereafter for as long as treatment continues.

Prescribing physicians must register themselves, their patients and a nominated pharmacist with the

Clozaril Patient Monitoring Service. This service provides for the required leucocyte counts as well as a drug supply audit so that Clozaril treatment is promptly withdrawn from any patient who develops abnormal leucocyte findings.

Each time Clozaril is prescribed, patients should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints or other symptoms which might suggest infection, such as fever or sore throat.

Precautions: Clozaril can cause agranulocytosis. The following precautionary measures are mandatory: Clozaril should not be used concurrently with drugs known to have a substantial potential to depress bone marrow function, such as co-trimoxazole, chloramphenicol, sulphonamides, pyrazolone analgesics, phenylbutazone, penicillamine, carbamazepine or cytotoxic agents. Concomitant use of long-acting depot antipsychotics (which have myelosuppressive potential) is not recommended because these medications cannot rapidly be removed from the body in situations where this may be required eg neutropenia.

Before starting Clozaril treatment, a white blood cell count and a differential count must be performed. Only patients with normal findings may receive the drug.

During Clozaril treatment the white blood cell count and differential count must be monitored weekly for the first 18 weeks and at least at two-week intervals thereafter. Monitoring must continue for as long as the patient is on the drug.

Particular attention should be paid to the white blood cell count and the differential count if any flu-like complaints or other symptoms develop which might suggest infection. Each time Clozaril is prescribed the patient should be reminded to contact the treating physician immediately if any kind of infection begins to develop.

If the white blood cell count falls below 3000/mm³ and/or the absolute neutrophil count drops below 1500/mm³, Clozaril must be withdrawn at once and the patient closely monitored. The patient must not be re-exposed to Clozaril.

In the event of an infection or a routine white blood cell count between 3000 and 3500/mm³ and/or a neutrophil count between 1500 and 2000/mm³, the patient should be re-evaluated immediately with respect to the white blood cell count and the differential count. Should there be a decline in either, Clozaril must be withdrawn at once. If the blood cell count remains the same or increases, treatment with Clozaril may continue provided that the leucocytes and granulocytes are checked at least twice weekly until it is certain that the patient has a stable leucocyte count within the range 3000 to 3500/mm³ or higher.

If Clozaril has been withdrawn and a further fall of white blood cell count below 1000/mm³ occurs and/or the neutrophils decrease below 500/mm³, the patient should be referred immediately for specialised care. Clozaril lowers the seizure threshold – see *'Dosage and administration – other special patient groups'*.

Orthostatic hypotension, with or without syncope, can occur with Clozaril treatment. Rarely, collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur during initial titration in association with rapid dose escalation; on very rare occasions they occurred even after the first dose. Therefore, patients commencing Clozaril treatment require close medical supervision.

Drowsiness may occur, especially at the beginning of therapy. Owing to its sedative action, Clozaril may impair the reactions of the patients e.g. when driving vehicles or operating machinery. Clozaril should be administered with caution to patients who participate in activities requiring complete mental alertness.

Clozaril exerts anticholinergic activity; therefore, careful supervision is indicated in the presence of prostatic enlargement, narrow-angle glaucoma and paralytic ileus.

In liver diseases, regular monitoring of liver function is necessary.

During Clozaril therapy patients may experience transient temperature elevations above 38°C, with a peak incidence within the first 3 weeks of treatment. This fever is generally benign. Occasionally, it may be associated with an increase or decrease in the WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered.

Drug interactions: Drugs known to have a substantial potential to depress bone marrow function should not be used concurrently with Clozaril (see *Precautions*, second paragraph).

Clozaril may enhance the central effects of alcohol, MAO inhibitors, CNS depressants including narcotics, benzodiazepines and antihistamines. Particular caution is advised when Clozaril therapy is initiated in patients who are receiving (or have recently received) a benzodiazepine or any other psychotropic drug, as these patients may have an increased risk of circulatory collapse, which, on rare occasions, can be profound and may lead to cardiac and/or respiratory arrest.

Because of the possibility of additive effects, caution in the concomitant administration of drugs with anticholinergic, hypotensive or respiratory depressant effects is essential.

Since clozapine is highly bound to plasma proteins, the administration of Clozaril to a patient taking another drug which is highly protein bound (e.g. warfarin) may cause an increase in plasma concentrations of this drug, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound clozapine by other highly protein-bound drugs.

Concomitant administration of cimetidine, a drug known to inhibit the cytochrome P450 enzyme system, may increase the plasma levels of clozapine, possibly resulting in adverse effects.

Concomitant administration of phenytoin, and possibly other drugs known to induce the cytochrome P450 enzyme system, may reduce the plasma levels of clozapine and may be associated with the recurrence of psychotic symptoms.

Concomitant use of lithium or other CNS-active agents may increase the risk of development of neuroleptic malignant syndrome (NMS).

In Clozaril-treated patients, the hypertensive effect of adrenaline and its derivatives may be reversed.

Use in pregnancy and lactation: The safe use of Clozaril in pregnancy has not been established and its use is not recommended. A return to normal menstrual cycling may occur as a result of switching from conventional neuroleptics to Clozaril, therefore adequate contraceptive measures must be ensured in women of child bearing potential.

Animal studies suggest that Clozaril is excreted in breast milk; therefore, mothers receiving Clozaril must not breast-feed.

Overdosage: Fatal overdoses have been reported with Clozaril mostly at doses above 2000 mg. There have also been reports of patients recovering from overdoses in excess of 4000 mg.

Signs and symptoms: drowsiness, lethargy, coma, areflexia, confusion, agitation, delirium, hyperreflexia, convulsions, hypersalivation, mydriasis, blurred vision, thermolability, tachycardia, hypotension, collapse, cardiac arrhythmias (in particular AV-block, extrasystoles), respiratory depression or failure.

Treatment: gastric lavage followed by the administration of activated charcoal within the first 6 hours after the ingestion of the drug. (Peritoneal dialysis and haemodialysis are not very effective.) Symptomatic treatment under continuous cardiac monitoring, sur-

veillance of respiration, monitoring of electrolytes and acid-base balance. The use of adrenaline and its derivatives should be avoided in the treatment of hypotension because of the possibility of a 'reverse adrenaline' effect. Close medical supervision is necessary for at least five days because of the possibility of delayed reactions.

Side-effects: Neutropenia leading to agranulocytosis is a risk of Clozaril treatment. This reaction, although generally reversible, can prove fatal. The majority of cases occur in the first 18 weeks of treatment. Because immediate withdrawal of the drug is required to prevent the development of life-threatening agranulocytosis, monitoring of the white blood cell count is mandatory (see 'Warning' and 'Precautions').

Patients on Clozaril may develop unexplained leucocytosis, including eosinophilia, especially in the initial weeks of treatment.

Central nervous system: drowsiness and sedation are among the most common side-effects observed. Dizziness or headache may also occur.

Clozaril lowers the seizure threshold in a dose-dependent manner and may cause EEG changes, including the occurrence of spike and wave complexes. Convulsions may, therefore, be precipitated in individuals who have epileptogenic potential but no previous history of epilepsy. If seizures occur while on Clozaril, treatment should be suspended for 24 hours and then resumed at a lower dose. It may be possible to control the problem by reducing the dosage and if necessary, raising it again very gradually. Anticonvulsant treatment may be considered but carbamazepine should be avoided because of its potential to depress bone marrow function, and with other anticonvulsant drugs the possibility of a pharmacokinetic interaction should be considered. On rare occasions it may induce episodes of delirium.

Extrapyramidal symptoms are limited mainly to tremor, akathisia and rigidity and if such effects occur, they tend to be mild and transient.

There have been several reported cases of neuroleptic malignant syndrome (NMS) in patients receiving Clozaril either alone or in combination with lithium or other CNS-active agents.

Autonomic nervous system: dry mouth, disturbances of accommodation and disturbances in sweating and temperature regulation have been reported. Hypersalivation is a common side-effect.

Cardiovascular system: tachycardia and postural hypotension, with or without syncope, may occur, especially in the initial weeks of treatment. Less commonly, hypertension may also occur. In rare cases profound circulatory collapse has been reported. ECG changes may occur and isolated cases of cardiac arrhythmias, pericarditis and myocarditis (with or without eosinophilia) have been reported, some of which have been fatal. Myocarditis can be difficult to diagnose as symptoms may be non-specific. Heart failure, arrhythmias or symptoms mimicking myocardial infarction or pericarditis may, however, be presenting features. Confirmation of diagnosis may not be possible but if suspicion is high, Clozaril medication should be stopped.

Gastro-intestinal system: nausea, vomiting and constipation may occur.

Increases in hepatic enzymes and, in rare cases, cholestasis have been reported.

Genito-urinary system: both urinary incontinence and retention and, in a few cases, priapism have been reported.

Miscellaneous: benign hyperthermia may occur, especially in the initial weeks of treatment (see 'Precautions').

Isolated reports of skin reactions have been received.

On rare occasions, hyperglycaemia has been reported in patients on Clozaril treatment.

Clozaril has not been associated with elevated prolactin levels.

With prolonged treatment considerable weight gain has been observed in some patients.

Sudden unexplained deaths are known to occur among psychiatric patients who receive antipsychotic medication as well as those who do not. Isolated cases of such deaths have been reported in patients receiving Clozaril.

Pharmaceutical precautions Nil.

Legal category POM.

Package quantities Containers of 84 tablets.

Further information

Clozaril Patient Monitoring Service: The use of Clozaril is restricted to patients who are registered with the Clozaril Patient Monitoring Service (CPMS). This service provides for the required leucocyte counts as well as a drug supply audit to ensure that Clozaril is withdrawn from any patient with an abnormal leucocyte count. Full details of the service are available from the Clozaril Patient Monitoring Service Manager at Sandoz Pharmaceuticals, Sandoz Pharmaceuticals (UK) Limited, Frimley Business Park, Frimley, Camberley, Surrey GU16 5SG. Tel: 0276 692255.

Supply of Clozaril is restricted to hospital pharmacies registered within the Clozaril Patient Monitoring Service.

Pharmacokinetics: The absorption of orally administered Clozaril is 90 to 95%; the rate or extent of absorption is not influenced by food.

Clozapine is subject to a moderate first-pass metabolism, resulting in an absolute bioavailability of 50 to 60%. In steady-state conditions, when given twice daily, peak blood levels occur on an average at 2.1 hours (range: 0.4 to 4.2 hours) and the volume of distribution is 1.6 l/kg. Clozapine is approximately 95% bound to plasma proteins. Its elimination is biphasic with a mean terminal half-life of 12 hours (range: 6 to 26 hours).

Clozapine is almost completely metabolised prior to excretion. Only trace amounts of unchanged drug are detected in the urine and faeces. Approximately 50% of the administered dose is excreted in the urine and 30% in the faeces in metabolised form.

Product licence numbers
25 mg tablets: 0101/0228
100 mg tablets: 0101/0229

4.8.2 Transparency of Licensing Action

From the perspective of consumer safety, the information given in patient information leaflets about specific medicinal products is more important to the consumer, as these leaflets warn of adverse reactions and contra-indications, than any information given about the operation of the legislative framework and the process by which medicinal products are regulated. However, the Author suggests that transparency about the operation of the legislative framework should be encouraged as it would make consumers more conscious of the means by which medicinal products are regulated and the organisations who are involved in regulating these products. There have, however, been problems in implementing this transparency and Meredith has commented:

> " To date consumer involvement in the regulatory process has been limited or non-existent [...] Patients need information about medicines to inform their choices about health care. Yet the imperatives of commercial confidentiality and protection of academic, professional and business interests reduce consumers' ability to find out about the history and potential benefits or disbenefits of both prescription only and over the counter medicines."[635]

There have been proposals in the past to make the licensing system in the UK more transparent. In 1992, Giles Radice MP, proposed a Private Member's Bill, the Medicines Information Bill, to reform section 118 of the Medicines Act 1968 and thereby allow greater public access to information about medicines and licensing decisions.[636] Also, in 1992, the Medicines Commission agreed to give out limited information about its meetings:

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[635] Meredith (1996).

[636] Pharmaceutical Journal (1992g), Lancet (1992d) and Kingman (1993). Section 118 deals with restrictions on disclosure of information obtained by an Inspector during the inspection of premises. The information which the Bill was concerned with (ie. information concerning licence applications) would be covered by commercial

> " in the interests of openness, within the constraints of the Medicines Act and common law requirements on confidentiality, to hold available after each meeting a summary of its proceedings for use in response to enquiries."[637]

However, the companies and medicinal products discussed are not identified, and the summaries are not published.

The National Consumer Council in its report "Secrecy and Medicines in Europe" commented:

> " Transparency and openness contribute to the better functioning of society's democratic institutions. Frequently, the pharmaceutical industry talks about having 'level playing fields' when it discusses trade and tariff issues. Transparency in its dealings and openness in terms of the information available about its products provide the best guarantee for companies and for consumers of level playing fields. When there are no secrets, no one has an unfair advantage, no one can abuse power."[638]

The NCC made the following recommendations:

> " 1. All information should be openly available *unless it can be proven* that its disclosure will infringe a company's commercial rights.
> 2. A multi-disciplinary working party should be established in order to develop a pragmatic and mutually acceptable working definition of the term 'commercial confidentiality'.
> 3. The summary assessment report should be taken as the current baseline for release of information about medicines.
> 4. All member states should publish and make publicly available a basis of approval document, using the guidelines to be developed for approvals granted by the EMEA.

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confidentiality.
[637]Medicines Commission et al (1993) p.6.
[638] NCC (1994) p48.

5. Consumers and professionals should have access to an on-line database for summary product characteristics.
6. Consumers and professionals should also have access to a register (such as the ECPHIN database) of approved indications for medicinal products. The register should be comprehensive, retrospective, and be regularly updated as products receive approvals for new indications, or as medicines are withdrawn from the market.
7. Suitably knowledgeable consumer representatives should be appointed to the CPMP and the CVMP, after nomination by consumer organisations."[639]

The Author agrees with the NCC's premise that consumers should have more access to information. The difficulty is in ensuring that the consumer is not bombarded with a plethora of information which makes little sense. This may have happened if consumers had been provided with the information suggested in the NCC's recommendations.

It is argued that the current situation regarding transparency is improving. The NCC's recommendations were made in 1994 and since then the Internet has proven to be a successful means of informing patients about the legislative framework. In 1996, Herxheimer (who has often been critical of the operation of the legislative framework) commented on improvements regarding the "transparency" of licensing decisions. In particular, he mentioned the publication of European Public Assessment Reports (EPARs) for all products approved under the Centralised Procedure and the issue of press releases relating to important decisions or statements made by the CPMP.[640] These EPARs and press releases are available in hard copy form and on the Internet.

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[639] Ibid pp48-50.
[640] Herxheimer (1996).

With regard to EPARs, the EMEA commented that they had:

> " proven to be a very important tool in providing both health professionals and consumers with the necessary information on centrally-authorised medicines which are available on the market. The number of requests for paper copies as well as the number of times that the website on the Internet has been visited was very high. The EPAR is a useful means of ensuring transparency and subjecting the EMEA's activities to effective public auditing."[641]

The EPAR for Rilutek manufactured by Rhône-Poulenc Rorer is given in Appendix XXV.

As discussed in Chapter 2,[642] the way forward is to make as much information as possible available to the public. The EMEA published an "Interim Report on the Consultation Exercise on Transparency and Access to Documents at the EMEA" in June 1997. One of the comments in this report was that the development of the Internet website was

> " an important example of the measure of transparency which the Secretariat has sought to bring to the work of the Agency."[643]

It was further stated in this Report that the web site has had 1.3 million "hits" and approximately 84,000 documents were downloaded (EPARs and guidelines were the most popular). It was mentioned earlier that the MCA plan to make more information available on their website. The Author suggests that this development is to be welcomed.

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[641] EMEA (1997a) p24.
[642] p64.
[643] EMEA (1997q)

4.9 The Promotion of Medicinal Products

4.9.1 Statutory Controls

The promotion of medicinal products by the pharmaceutical industry has two functions:

> " One is the directly commercial one of selling each firm's products and the other, that of informing the doctor about new medicines and developments in therapeutics."[644]

This promotion has been criticised by the media on a number of occasions[645] and the ethical implications of the relationship between the pharmaceutical industry and medical profession has been the subject of much discussion in the medical press.[646] One author stated:

> " I believe that seeing detailers [medical representatives] is detrimental to the practice of good medicine and that the best interests of both doctors and their patients would be served if physicians had nothing further to do with detailers."[647]

Another commented on the increasing influence of the pharmaceutical industry in the sponsorship of medical education:

> " We physician-educators are losing the battle for the hearts and minds of our house staff, whose stomachs are already full of pizza from pharmaceutical companies. Faculty resistance diminishes as one by one we join the speaker

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[644]Committee of Enquiry into the Relationship of the Pharmaceutical Industry with the National Health Service (1967) p63.

[645]Television programmes criticising promotional activities have included "First Tuesday" ("Sweetening the Medicine") broadcast on 6 November 1990 and newspaper reports have appeared in The Sunday Times (7, 14 and 21 November 1993), The Guardian (10 September 1986 and 21 August 1989), The Observer (19 July 1992) and The Sunday Sport (8 March 1987). Promotion by pharmaceutical companies in "Third World" countries has been criticised by Medawar and Freese (1982), Health Action International (1982a), Health Action International (1982b), Medawar ((1985), Breckenridge (1986), Greenhalgh (1986), Lancet (1993) and Collier and Fox (1993)

[646]Rosner (1989), Carlson (1990), Chren et al (1989), Waud (1992), Medawar (1989), and Harvey (1988).

[647]Lexchin (1989) p676.

> circuits delivering messages acceptable to industry - messages perhaps slightly bent by repetition and generous honorariums."[648]

A general practitioner in the Republic of Ireland analysed his meetings with sales representatives from 41 pharmaceutical companies over a one year period.[649] In total, he received 109 visits from 49 representatives. During these visits, he was given 174 samples worth £1485 and a number of gifts including stationery, pens, diaries, calendars, mugs, tapes, towels, a clothes brush, a desk tidy, an air freshener, an ice scraper and flower seeds. The information he was offered consisted of advertising brochures in 51 of the visits, data sheets in 11 of the visits and two representatives offered copies of journal articles. It was not suggested that the number of visits, gifts or samples he received was unusual. He commented:

> " Representatives are perceived by the industry as having a dual role as educators and promoters. During the visits I received, however, the emphasis was on promotion. [...] The gifts I received were not expensive items. Their main purpose seemed to be an attempt to keep a product's name before me, presumably in the hope that this would be consciously or unconsciously assimilated. Acceptance of gifts can have complex practical and ethical repercussions, including the establishment of a relationship in which a doctor may feel obliged to respond."[650]

In 1967, the Sainsbury Committee examined the promotion of medicinal products as part of a general review of the relationship of the pharmaceutical industry with the National Health Service.[651] The Committee investigated advertising in journals, promotional literature, the use of samples and the activities of sales representatives. The Committee found that the standards of promotion varied greatly between

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[648]Noble (1992) p363.
[649]O'Mahony (1993).
[650]Ibid p1649.
[651]Committee of Enquiry into the Relationship of the Pharmaceutical Industry with the National Health Service (1967).

pharmaceutical companies. In particular, the Committee received much evidence which was critical of the promotional literature sent to doctors:

> " The Royal College of General Practitioners described much of the literature as 'bad - seemingly in the form of cheap publicity, with inaccurate claims, lack of contra-indications and good references, lack of price..'. The British Medical Association told us that the main disadvantage to doctors was the absence of any 'independent medical control or scrutiny over the literature.' From the hospital authorities we received complaints of 'repetitive and uninformative literature' and of literature 'which does not contribute to existing knowledge of a product', and of 'highly coloured advertising matter reminiscent of detergent propaganda, which advocates the use of a drug but gives little or no information on dosage, action and reaction.'"[652]

The Committee recommended that the Medicines Commission should be given the responsibility to ensure that all promotional material given to doctors was impartial, complete and as accurate as possible. The Committee also proposed the introduction of "control documents", which would contain information relating to medicinal products, such as dosage, side effects and contra-indications, and could be used by the Medicines Commission to assess the accuracy of information contained in advertisements. It was also suggested that copies of control documents should be sent to doctors and pharmacists.

Following on from the report of Sainsbury Committee, part VI of the Medicines Act 1968 (sections 92 to 97) introduced controls to deal with the promotion of medicinal products.[653] The Medicines Commission was not given any powers to

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[652]Ibid p67.

[653] Medicines Division (1978a), Medicines Division (1983d), Medicines Control Agency (1990i) and Harrison (1987a) (chapters 18 to 20), examine the legislative provisions in detail. Harrison (1987a) also outlined earlier proposals and legislation, such as the Venereal Diseases Act 1917 and Cancer Act 1939, which prohibited advertisements relating to these diseases.

scrutinise advertisements, however, the proposal for "control documents" was adopted in provisions made relating to data sheets.

Section 92 sets out various definitions, crucial to the interpretation of the subsequent sections. "Advertisement" is defined as including:

> " every form of advertising, whether in a publication, or by the display of any notice, or by means of any catalogue, price list, letter (whether circular or addressed to a particular person) or other document or by words inscribed on any article, or by the exhibition of a photograph or a cinematograph film, or by way of a sound recording, sound broadcasting or television, or in any other way, and any reference to the issue of an advertisement shall be construed accordingly."[654]

"Advertisement" does not include spoken words except:

> " (a) words forming part of a sound recording or embodied in a soundtrack associated with a cinematograph film, and
>
> (b) words broadcast by way of sound broadcasting or television or transmitted to subscribers to a diffusion service.'[655]

"Advertisement" also does not include:

> " (a) the sale or supply, or offer or exposure for sale or supply, of a medicinal product in a labelled container or package;
>
> (b) the supply, with a medicinal product of any description, of a leaflet relating solely to medicinal products of that description."[656]

"Representation" is defined as:

> " any statement or undertaking (whether constituting a condition or a warranty or not) which consists of spoken words other than words falling within paragraph (a) or paragraph (b) of subsection (2) of this section."[657]

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[654]Section 92(1).
[655]Section 92(2).
[656]Section 92(3).
[657]Section 92(5).

Section 93 deals with false or misleading advertisements and representations, and creates the following offences:

- the issue of a false or misleading advertisement;[658]
- the issue of an advertisement containing an unauthorised recommendation for the use of a medicinal product;[659]
- making a false or misleading representation;[660]
- making a representation which refers to an unauthorised recommendation for the use of a medicinal product;[661]

An advertisement or a representation is taken to be false and misleading if

" (a) it falsely describes the description of medicinal products to which it relates, or

(b) it is likely to mislead as to the nature or quality of medicinal products of that description or as to their uses or effects."[662]

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[658]"Any person who, being a commercially interested party, or at the request or with the consent of a commercially interested party, issues, or causes another person to issue, a false or misleading advertisement relating to medicinal products of any description shall be guilty of an offence." - Section 93(1).

[659]"Where a licence under Part II of this Act is in force which is applicable to medicinal products of a particular description, and, in accordance with the provisions of the licence, the purposes for which medicinal products of that description may be recommended to be used are limited to those specified in the licence, then, subject to the following provisions of this section, any person who, being a commercially interested party, or at the request or with the consent of a commercially interested party, issues, or causes another person to issue, an advertisement relating to medicinal products of that description which consists of or includes unauthorised recommendations shall be guilty of an offence." - Section 93(2).

[660]"Any person who in the course of a relevant business carried on by him, or while acting on behalf of a person carrying on such a business, makes a false or misleading representation relating to a medicinal product in connection with the sale. or offer for sale, of that product shall be guilty of an offence; and any person, who, in the course of such a business, makes a false or misleading representation relating to medicinal products of a particular description -

(a) to a practitioner for the purpose of inducing him to prescribe or supply medicinal products of that description, or

(b) to a patient or client of a practitioner for the purpose of inducing him to request the practitioner to prescribe medicinal products of that description, or

(c) to a person for the purpose of inducing him to purchase medicinal products of that description from a person selling them by retail,

shall be guilty of an offence." - Section 93(3).

[661]"Where in the circumstances specified in subsection (2) of this section any person, in the course of a relevant business carried on by him, or while acting on behalf of a person carrying on such a business, -

(a) in connection with the sale, or offer for sale, of a medicinal product of the description in question, makes a representation relating to the product which consists of or includes unauthorised recommendations, or

(b) for any such purpose as is specified in paragraphs (a) to (c) of subsection (3) of this section makes a representation relating to medicinal products of that description which consists of or includes unauthorised recommendations,

that person, subject to the following provisions of this section, shall be guilty of an offence."- Section 93(4).

[662]Section 93(7).

The requirement that advertisements and representations must be consistent with the recommendations for the uses of a medicinal product contained in its product licence was described as being one of the most important features of the Medicines Act.

> " It is the vital link that enables the Licensing Authority to ensure that any stipulations considered necessary by the expert committee, or the Medicines Commission, in relation to the uses for which a medicine is to be promoted, or any notice that has to be given of any important side effects are not disregarded when the drug is actually promoted, either to a practitioner or to the public." [663]

Section 93 also provides two defences:

- that the person charged with the offence did not know, and could not with reasonable diligence have discovered, that the advertisement or representation was false or misleading, or included unauthorised recommendations[664]; and
- that the person charged with the offence is in the business of issuing or arranging for the issue of advertisements (e.g. an advertising agency) and that he did not know and had no reason to suspect that the issue of the advertisement would amount to an offence.[665]

Section 94 creates another offence and states that an advertisement cannot be issued without the consent of the product licence holder. Section 95 gives the "appropriate Ministers" the power to regulate advertisements and representations. This power has been used in relation to medicinal products with product licences of right,[666] advertisements issued in professional journals,[667] advertisements directed at medical and dental practitioners[668], advertising direct to the public[669] and the advertising of

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[663]Official Report, 5th Series, Commons, vol. 758 col. 1604 (15 February 1968). This comment was made by the Minister of Health during the Second Reading of the Medicines Bill.
[664]Section 93(5).
[665]Section 93(6).
[666]The Medicines (Advertising of Medicinal Products) Regulations 1975 (S.I. No. 298).
[667]The Medicines (Advertising of Medicinal Products) Regulations 1975 (S.I. No. 1326).
[668]The Medicines (Advertising to Medical and Dental Practitioners) Regulations 1978 (S.I. No. 1020).
[669]The Medicines (Labelling and Advertising to the Public) Regulations 1978 (S.I. No. 41).

fluids for contact lenses.[670] The Ministers can prohibit the issue of advertisements or the making of representations, and impose requirements for the following purposes:

" (a) securing that adequate information is given with respect to medicinal products;

(b) preventing the giving of misleading information with respect to such products;

(c) promoting safety in relation to such products."[671]

The Licensing Authority has also been given powers to control advertising by invoking standard provisions relating to advertising, which are contained in every product licence.[672]

Section 96 contains provisions relating to advertisements and representations directed at practitioners, which require:

" (a) that a data sheet relating to medicinal products of the description in question is sent or delivered to the practitioner with the advertisement, or is delivered to him at the time when the representation is made, or that such a data sheet has been sent or delivered to him not more than fifteen months before the date on which the advertisement is sent or delivered or the representation is made, and

(b) that the advertisement or representation is not inconsistent with the particulars contained in the data sheet."

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[670]The Medicines (Contact Lens Fluids and Other Substances)(Advertising and Miscellaneous Amendments) Regulations 1979 (S.I. No.1760).

[671]Section 95(4).

[672]The Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (S.I. No. 972) and The Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1974 (S.I. No. 1523).
Paragraph 9:
"The Licensing Authority may notify a licence holder that advertisements may not include particulars relating to the uses, nature or effects of the product unless they are in accordance with the product licence or the application for the licence..."
Paragraph 10:
"The Licensing Authority may require the licence holder to provide details of planned advertisements prior to issue."
Paragraph 11:
"The Licensing Authority may prohibit the issue of particular advertisements, require an advertisement to be modified or require particular warnings or precautions to be included in an advertisement..."

In 1975, the annual report of the Medicines Division reported that the Division had taken an "active interest" in the content of advertisements:

> " A modest programme of inspecting advertisements in professional and popular journals was undertaken, and a group of doctors, pharmacists, lawyers and administrators within the Division met regularly to consider individual cases of unsatisfactory advertisements found in this way or brought to the attention of the Department by people outside."[673]

On 28 April 1977, following consideration by the Medicines Commission and discussions between the Government and the Association of the British Pharmaceutical Industry (ABPI), the Secretary of State for Social Services announced that advertising would be controlled by a combination of statutory and voluntary regulations.[674] The ABPI agreed to strengthen its Code of Practice, appoint independent members to its Code of Practice Committee and regularly scrutinise a sample of published advertisements. In 1978, the Medicines Division made arrangements with the Proprietary Association of Great Britain (PAGB), the British Herbal Medicines Association and the Health Food Manufacturers Association, with regard to promoting further self-regulatory control in the form of vetting advertisements prior to publication.[675]

In 1978, the Medicines Division scrutinised 32 advertisements and commented:

> " The number of advertisements being brought to the Group's [Advertising Action Group] attention has been declining steadily over the last two years. It is evident that there has been a considerable improvement in the standards of advertising of medicinal products, both to the public and to practitioners. Much of this improvement is due to the adherence by members of various trade associations to

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[673]Medicines Commission et al (1976) p76.
[674]Ibid p96.
[675]Medicines Commission et al (1979) p102.

> their Codes of Practice, and to the vigilance of those administrators, who keep a close watch on advertisements."[676]

However, in 1981, the Medicines Division issued a warning regarding the promotion of certain medicinal products.[677] A further warning was issued in 1983 and it pointed out that most of the offending advertisements had not been cleared through code of practice committees. There were three main areas of complaint:

- the promotion of a product for indications wider than those specified in the product licence.
- advertising in anticipation of approval being given by the Licensing Authority to a variation in a product licence.
- claims made for a product without hard evidence to support them.[678]

In 1983, Jack Ashley MP criticised the failure of the Department of Health and Social Security to "ensure the fairness and factual accuracy" of advertising and also expressed concern about the Department's random and non-comprehensive scrutiny of advertisements.[679] In 1984, this lack of comprehensive scrutiny was also criticised by the Sunday Times, which cited it as the reason why many "infringements of the law" were not corrected.[680] The Sunday Times also mentioned that there had been very few prosecutions for advertising offences.

Appendix XXVI lists every successful prosecution in respect of advertising offences, as reported in the MAIL series in the period 1973 to 1997.[681]

In 1994, Council Directive 92/28/EEC concerning the advertising of medicinal products was implemented by The Medicines (Advertising) Regulations 1994 and

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[676]Ibid p101.
[677]Medicines Division (1981c).
[678]Medicines Division (1983g).
[679]Pharmaceutical Journal (1983dd).
[680]Pharmaceutical Journal (1984r).

The Medicines (Monitoring of Advertising) Regulations 1994. These new regulations amended the provisions in the Medicines Act.[682]

Regulation 3 of these Regulations prohibits the issue of an advertisement for a medicinal product which has no product licence and Regulation 4 sets out the duties of licence holders including the requirements that they must ensure that medical sales representatives are adequately trained.[683] Part III of the Regulations applies to advertisements which are wholly or mainly directed at members of the general public. Regulation 6 prohibits the advertisement of products for certain specified diseases.[684] Regulation 9 prohibits the use of certain material in advertisements. For example, advertising which suggests that the effects of taking a medicinal product are guaranteed, are unaccompanied by side effects or are better than, or equivalent to, those of another identifiable treatment or medicinal product.[685]

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[681] Also *Roussel Laboratories Limited and Another*, Court of Appeal (Criminal Division), (1988) 88 Cr App Rep 140.

[682] "Advertisement" has the same meaning assigned to it by Section 92 of the Medicines Act, except that in relation to a relevant medicinal product -
(a) provided that it makes no product claim, reference material, a factual, informative statement or announcement, a trade catalogue or a price list shall not be taken to be an advertisement, and
(b) an advertisement includes a representation.

[683] (a) establish a scientific service to compile and collate all information, whether received from medical sales representatives employed by him or from any other source, relating to that product;
(b) ensure that, in relation to any such product which medical sale representatives promote, those medical sales representatives are given adequate training and have sufficient scientific knowledge to enable them to provide information which is as precise and as complete as possible about that product;
(c) whenever required to do so by the licensing authority, furnish particulars of any advertisement or proposed advertisement for which he is responsible relating to that product, including particulars as to the contents and form of the advertisement, the method of dissemination and the date of first dissemination; and
(d) ensure that, in relation to an advertisement relating to that product, any decision taken by the licensing authority is immediately and fully complied with.

[684] In Schedule 1, there is a list of these diseases or classes of disease:
"bone diseases; cardiovascular diseases; chronic insomnia; diabetes and other metabolic diseases; diseases of the liver, biliary system and pancreas; endocrine diseases; genetic disorders; malignant diseases; psychiatric diseases; serious disorders of the eye and ear; serious gastrointestinal diseases; serious infectious diseases, including HIV-related diseases and tuberculosis; serious neurological and muscular diseases; serious renal diseases; serious respiratory diseases; serious skin disorders; and sexually transmitted diseases."

[685] Regulation 9:
(a) gives the impression that a medical consultation or surgical operation is unnecessary, in particular by offering a diagnosis or by suggesting treatment by post, fax or telephone,
(b) suggests that the effects of taking the medicinal product are guaranteed, are unaccompanied by side effects or are better than, or equivalent to, those of another identifiable treatment or medicinal product,
(c) suggests that health can be enhanced by taking the medicinal product,
(d) suggests that health could be affected by not taking the medicinal product,
(e) is directed exclusively or principally at children,

Part IV of the Regulations sets out provisions relating to advertising to health professionals. Regulation 14 states that no person shall issue an advertisement unless it contains "essential information compatible with the summary of product characteristics" and the "specified particulars" set out in Schedule 2 to the Regulations.[686]

Regulation 20 sets out provisions relating to the activities of medical sales representatives, including the requirement on these representatives to provide a copy of the summary of product characteristics for the medicinal product they are promoting. A breach of this regulation, on indictment, could incur an unlimited fine and/or imprisonment not exceeding 2 years. A breach of this regulation, on summary conviction, would incur a fine up to £5,000.

(f) refers to a recommendation by scientists, health professionals or persons who are neither of the foregoing but who, because of their celebrity, could encourage the consumption of medicinal products.
(g) suggests that the medicinal product is a foodstuff, cosmetic or other consumer product,
(h) suggests that the safety or efficacy of the medicinal product is due to the fact that it is natural,
(i) might, by a description or detailed representation of a case history, lead to erroneous self-diagnosis,
(j) refers, in improper, alarming or misleading terms, to claims of recovery,
(k) uses, in improper, alarming or misleading terms, pictorial representations of changes in the human body caused by disease or injury, or of the action of a medicinal product on the human body or parts thereof, or
(l) mentions that the medicinal product has been granted a product licence.

[686] Schedule 2 contains the following provisions:

" 1. The licence number of the medicinal product.
2. The name and address of the holder of the product licence which relates to the medicinal product or the business name and address of the part of his business that is responsible for its sale or supply.
3. The supply classification of the medicinal product, specifying whether the product is a medicinal product for supply by prescription only, a medicinal product on a general sale list, or a pharmacy medicinal product.
4. The name of the product, and a list of the active ingredients using the common name placed immediately adjacent to the most prominent display of the name of the product.
5. One or more of the indications for the product consistent with the terms of the licence.
6. A succinct statement (where relevant) of the entries in the summary of product characteristics or, if there is no summary of product characteristics, the data sheet, relating to side effects, precautions and relevant contra-indications.
7. A succinct statement of the entries in the summary of product characteristics or, if there is no summary of product characteristics, the data sheet, relating to dosage and method of use relevant to the indications shown. The method of administration should also be shown where there is not obvious.
8. A warning issued by the licensing authority under Part II of the Act which is required to be included in advertisements.
9. The cost (excluding value added tax) of either a specified package of the medicinal product to which the advertisement relates, or a specified quantity or recommended daily dose, calculated by reference to any specified package of the product, except that such cost may be admitted in the case of an advertisement inserted in a publication which is printed in the United Kingdom but with a circulation outside the United Kingdom of more than 15 per cent of its total circulation.
10. The particulars contained in paragraphs 6, 7 and 8 shall be printed in a clear and legible manner and be placed in such a position in the advertisement that their relationship to the claims and indications for the product can readily be appreciated by the reader."

Regulation 21(1) deals with inducements and hospitality:

> " Where relevant medicinal products are being promoted to persons qualified to prescribe or supply relevant medicinal products, no person shall supply, offer or promise to such persons any gift, pecuniary advantage or benefit in kind, unless it is inexpensive and relevant to the practice of medicine or pharmacy."

Regulation 21(1) does not prevent:

> " any person offering hospitality (including the payment of travelling or accommodation expenses) at events for purely professional or scientific purposes to persons qualified to prescribe or supply relevant medicinal products, provided that -
>
> (a) such hospitality is reasonable in level,
>
> (b) it is subordinate to the main scientific objective of the meeting, and
>
> (c) it is offered only to health professionals."

Conditions (a) to (c) also apply to hospitality at a meeting or event held for the promotion of a medicinal product.

Regulation 21(5) specifies:

> " No person qualified to prescribe or supply relevant medicinal products shall solicit or accept any gift, pecuniary advantage, benefit in kind, hospitality or sponsorship prohibited by this regulation."

A breach of this regulation could incur a fine up to a maximum of £5,000.

Regulation 4 of The Medicines (Monitoring of Advertising) Regulations 1994 specifies that it is the duty of the Licensing Authority to consider complaints about advertisements for medicinal products.[687] However, Regulation 5 specifies that the Licensing Authority may, with the agreement of the complainant, specify that the

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[687] S.I. 1994/1933

complaint should be dealt with by "a self-regulatory body which deals with complaints about advertisements".

There have been no reported cases in the MAIL series relating to prosecutions under the Medicines (Advertising) Regulations 1994. However, this situation may change as, in 1997, the Government announced a "clampdown" on pharmaceutical companies and wholesalers who offer gifts and inducements. Baroness Jay commented:

> " Examples of unlawful promotions include 'bonus points' entitling health professionals to gifts like air miles, holiday discounts, mountain bikes, electrical and photographic goods, prize draws, and competitions offering exotic holidays as prizes.
>
> It is completely unacceptable for pharmaceutical companies to encourage health professionals to use their products, through free gifts and other 'sweeteners'.
>
> The vast majority of health professionals make decisions solely on the basis of their patients' interests. The public does not expect them to be influenced by incentives to prescribe or supply particular medicines.
>
> I do not want anyone to be in any doubt that we will not tolerate unlawful promotions which seek to exert improper influence and that enforcement action under the criminal law will be taken against offenders."[688]

Also, the MCA sent a letter to "industry and professional bodies" to "remind those involved in the promotion of relevant medicinal products and those prescribing or supplying medicines of their obligations under the law."[689] It was remarked in an Editorial in the Pharmaceutical Journal that:

> " It is not promotions that might influence doctors' clinical decisions that the MCA sees as the current problem. Such activities are generally kept well in check by the Association of the British Pharmaceutical Industry code of practice without

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[688] DoH press release 28/7/97 - taken from the DoH web site.

the need for action by the MCA. What the MCA is principally concerned about is a comparatively recent phenomenon - the offer of substantial gifts and inducements to pharmacists by generic manufacturers, distributors and wholesalers. Many of the promotional schemes run by such companies clearly infringe the Regulations, says the MCA. And if the companies are infringing the law, then pharmacists who accept the gifts are also committing a criminal offence and could face large fines or even prison sentence."[690]

Following these announcements, in August 1997, the MCA issued a consultation document, MLX 239, "Strengthening of Advertising Controls by the Amendment of Existing Regulations."[691] The proposed amendments to the current regulations are summarised as follows:

" - clarifying the meaning of 'persons qualified to prescribe or supply' by stating that it includes persons who may lawfully sell or supply medicines;

- a requirement for products authorised by the Community in accordance with Council Regulation (EEC) No. 2309/93 to comply with the Advertising Regulations;

- a prohibition backed up by a criminal penalty on the issue of an advertisement which does not comply with the particulars listed in the summary of product characteristics;

- a prohibition on the supply for promotional purposes of medicines to the public, whether unsolicited or not. This will cover free samples; and

- powers of the Medicines Control Agency backed up by criminal sanctions to prevent advertisements and prevent the republishing or publishing of advertising material which it considers to be in breach of the Advertising Regulations. This provision replaces that in Regulation 4 (c) of the Advertising Regulations."[692]

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[689] MCA (1997g)
[690] Pharmaceutical Journal (1997f).
[691] MCA (1997h).
[692] Ibid.

These amendments have not yet been enacted by statutory instrument. In the opinion of the Author, a strengthening of the controls on advertising is to be encouraged as it is in the interests of consumer safety for medicinal products to be supplied on the basis of benefit to the patient as opposed to occurring on the basis of advertising or any other promotional practice.

4.9.2 The Code of Practice for the Pharmaceutical Industry

Self-regulation by the pharmaceutical industry plays a major role in the regulation of the promotional practices utilised by the pharmaceutical industry. The Editorial in the Pharmaceutical Journal, as quoted in the previous section, stated that promotional activities are kept "generally well in check" by the ABPI. The most recent version of the Code of Practice for the Pharmaceutical Industry issued by the ABPI came into force on 1 January 1996.

The Code is administered by the Prescription Medicines Code of Practice Authority (PMCPA), which was established in 1993, and replaced the Code of Practice Committee. The PMCPA consists of a Director, Secretary and Deputy Secretary. There is also a Code of Practice Appeal Board which comprises: an independent legally qualified Chairman; three independent medical members appointed in consultation with the British Medical Association, one with recent experience as a general practitioner and one with recent experience as a hospital consultant; four medical directors or medically qualified senior executives from pharmaceutical companies; one independent pharmacist appointed following consultation with the Royal Pharmaceutical Society of Great Britain; one member from an independent body involved in providing information on medicines; and eight directors or senior executives from pharmaceutical companies.

The aim of the Code of Practice is :

" to ensure that the promotion of medicines to members of the health professions and to appropriate administrative staff is carried out in a responsible, ethical and professional manner. The Code recognises and seeks to achieve a balance between the needs of patients, industry, health professionals and the general public, bearing in mind the political and social environment within which the industry operates and the statutory controls governing medicines." [693]

The Code also incorporates the principles set out in the International Federation of Pharmaceutical Manufacturers Associations' "Code of Pharmaceutical Marketing Practices", the European Federation of Pharmaceutical Industries' Associations' "European Code of Practice for the Promotion of Medicines", the European Community Directive on the advertising of medicinal products for human use and the World Health Organisation's "Ethical Criteria for Medicinal Drug Promotion".[694]

Clause 1 sets out the scope of the Code and defines certain terms. The Code applies to:

" the promotion of medicines to members of the United Kingdom health professions and to appropriate administrative staff and to information made available to the general public about medicines so promoted.

It does not apply to the promotion of over-the-counter medicines to members of the health professions when the object of that promotion is to encourage their purchase by members of the general public." [695]

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[693]PMCPA (1996).
[694]Ibid p4.
[695]Ibid p5.

Promotion is defined by the Code as:

" any activity undertaken by a pharmaceutical company or with its authority which promotes the prescription, supply, sale or administration of its medicines. It includes:

- journal and direct mail advertising;
- the activities of representatives including detail aids and other printed material used by representatives;
- the supply of samples;
- the provision of inducements to prescribe, supply or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind;
- the provision of hospitality for promotional purposes;
- the sponsorship of promotional meetings;
- the sponsorship of scientific meetings including payment of travelling and accommodation expenses in connection therewith;
- the provision of information to the general public either directly or indirectly; and
- all other sales promotions in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems and the like." [696]

It does not include:

" - replies made in response to individual enquiries from members of the health professions or in response to specific communications whether of enquiry or comment, including letters published in professional journals;
- factual, informative announcements and reference material relating, for example, to pack changes, adverse reaction warnings, trade catalogues and price lists, provided they include no product claims;

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[696]Ibid.

- measures or trade practices relating to prices, margins or discounts which were in existence on 1 January 1993;
- data sheets, the contents of which are determined by Regulations made under the Medicines Act 1968 and summaries of product characteristics as provided for in EC Directive 65/65;
- the labelling on medicines and accompanying package leaflets insofar as they are not promotional for the medicines concerned; the contents of labels and package leaflets;
- statements relating to human health or diseases provided there is no reference, either direct or indirect, to specific medicines." [697]

[697] Ibid.

4.9.3 Analysis of Breaches of the Code of Practice

Since 1983, reports of breaches of the Code of Practice have been published by the Code of Practice Committee and latterly by the PMCPA.[698]

Table 30 Reports of Alleged Breaches of the Code of Practice (1983 -1996)

YEAR	TOTAL NUMBER OF CASES	BREACH OF THE CODE
1983	39	25
1984	54	32
1985	48	33
1986	52	36
1987	48	28
1988	57	36
1989	74	51
1990	105	72
1991	74	38
1992	84	50
1993	81	48
1994	145	80
1995	104	51
1996	102	65

From Table 30, it can be observed that there has been a steady rise in the numbers of cases which have been reported as having allegedly breached the Code of Practice. It is unclear whether this increase is due to a perceived decline in the standard of promotional practices used by the pharmaceutical industry or whether there has been an improvement in the reporting these alleged breaches. Certainly, the PMCPA have adopted a more "transparent" attitude to their investigation of alleged breaches and this may have encouraged health professionals and others to report suspected breaches.[699]

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[698] Listed under PMCPA and Code of Practice Committee in the bibliography.
[699] PMCPA (1996b).

Appendix XXVII present an analysis of the above cases including the medicinal products involved, the complainants involved, the companies which have breached the Code and the sections of the Code which were breached.[700]

The medicinal products referred to in Table A of Appendix XXVII are as described in the case reports. Where different formulations of medicinal products have been involved these have been listed separately. The medicinal product which has breached the Code of Practice most often is Zovirax, which is manufactured by Wellcome (now Glaxo-Wellcome).

The complainants listed in Table B in Appendix XXVII have been divided into four categories: health professionals; companies; the PMCPA; and miscellaneous. The complainants are listed as they appear in the original case reports. Several of the companies mentioned have several subsidiaries or have merged with other companies, and references to them could have been amalgamated, and some of the health professionals' designations could have been amalgamated. However, in both instances, it was decided to report the complainants as they were designed in the original case reports.

This table illustrates that most complaints come from health professionals and, in particular, general practitioners. Occasionally, it can be sensed from the reports that rival pharmaceutical companies seem to be engaging in "tit-for-tat" complaints to the PMCPA. For example, Leo Ltd and E. Merck Ltd both promoted treatment for psoriasis and both complained about the other's promotional practices to the PMCPA.[701]

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[700]These tables have been updated to include material reported in the most recent edition of the Code of Practice Review in August 1997.
[701] PMCPA (1996c).

Table C in Appendix XXVII lists the companies which have breached the Code of Practice. Lederle Laboratories have breached the Code most often with a total of 30 complaints. Table D in Appendix XXVII presents an analysis of the breaches of the Code of Practice from 1983 to 1996.[702]

A breach of Clause 2, "Methods of Promotion" of the Code of Practice is arguably the most serious breach of the Code of Practice:

> " Methods of promotion must never be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry."[703]

It is explained in the Code that a ruling in breach of this clause is a sign of particular censure and is reserved for such circumstances. No other clause in the Code of Practice is referred to by the PMCPA in these terms. This clause has been breached a total of 50 times. Another important clause is Clause 3, which relates to "Marketing Authorisations":

> " 3.1 A medicine must not be promoted prior to the grant of the marketing authorisation which permits its sale or supply."
>
> " 3.2 The promotion of a medicine must be in accordance with the terms of its product licence and must not be inconsistent with the particulars listed in its summary of product characteristics or data sheet."[704]

This has been breached 27 times.

The most breached clause of the Code of Practice is Clause 7 "Information, Claims and Comparisons", which has been breached 640 times:

> " 7.1 Upon reasonable request, companies must promptly provide members of the health professions and appropriate administrative staff with accurate and relevant information about the medicines which the company markets.

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[702] Over this period, the Code of Practice has been revised and the clause numbers in small capitals refer to the 1996 edition of the Code; the clause numbers in italics refer to an earlier version of the Code.
[703] PMCPA (1997f) p6.

7.2 Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication.

7.3 Any information, claim or comparison must be capable of substantiation.

7.4 Substantiation for any information, claim or comparison must be provided without delay at the request of members of the health professions or appropriate administrative staff. It need not be provided, however, in relation to the validity of indications approved in the marketing authorisation.

7.5 When promotional material refers to published studies, clear references must be given.

7.6 All artwork including illustrations, graphs and tables must conform to the letter and spirit of the Code. Graphs and tables must be presented in such a way as to give a clear, fair, balanced view of the matters with which they deal, and must not be included unless they are relevant to the claims or comparisons being made.

7.7 Information and claims about side-effects must reflect available evidence or be capable of substantiation by clinical experience. It must not be stated that a product has no side-effects, toxic hazards or risks of addiction. The word "safe" must not be used without qualification.

7.8 Exaggerated or all-embracing claims must not be made and superlatives must not be used except for those limited circumstances where they relate to a clear fact about a medicine. Claims should not imply that a medicine or active ingredient has some special merit, quality or property unless this can be substantiated.

7.9 The word "new" must not be used to describe any product or presentation which has been generally available, or any therapeutic indication which

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[704] Ibid.

> has been generally promoted, for more than twelve months in the United Kingdom.
>
> 7.10 Brand names of other companies' products must not be used unless the prior consent of the proprietors has been obtained."[705]

Clause 7.2 which refers to information, claims and comparisons being accurate, balanced, fair, objective, unambiguous and based on an up-to-date evaluation of evidence has been particularly breached. Indeed, additional advice is given in the Code regarding areas where particular care should be taken by companies in relation to this clause.[706]

Another important clause is Clause 15, "Representatives" and this has been breached 60 times:

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[705] Ibid pp12-13.

[706] " • *claims for superior potency in relation to weight* are generally meaningless and best avoided unless they can be linked with some practical advantage e.g. reduction in side-effects or cost of effective dosage.
- *the use of data derived from in-vitro studies, studies in healthy volunteers and in animals.* Care must be taken with the use of such data so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there is data to show that it is of direct relevance and significance.
- *economic evaluation of medicines.* The economic evaluation of medicines is a relatively new science. Care must be taken that any claim involving the economic evaluation of a medicine is borne out by the data available and does not exaggerate its significance.
  To be acceptable as the basis of promotional claims, the assumptions made in an economic evaluation must be clinically appropriate and consistent with the Marketing Authorisation. Attention is drawn to guidance on good practice in the conduct of economic evaluation of medicines which has been given by the Department of Health and the ABPI and which is available upon request from the Prescription Medicines Code of Practice Authority.
- *emerging clinical or scientific opinion.* Where a clinical or scientific issue exists which has not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue is treated in a balanced manner in promotional material.
- *hanging comparisons* whereby a medicine is described as being better or stronger or suchlike without stating that with which the medicine is compared must not be made.
- *price comparisons.* Price comparisons as with any comparison must be accurate, fair and must not mislead. Valid comparisons can only be made where like is compared with like. It follows therefore that in making a price comparison should be made on the basis of the equivalent dosage requirement for the same indications. For example, to compare the cost per ml for topical preparations is likely to mislead unless it can be shown that their usage rates are similar or, where this is not possible, for the comparison to be qualified in such a way as to indicate that usage rates may vary.
- *statistical information.* Care must be taken to ensure that there is a sound statistical basis for all information, claims and comparisons in promotional material. Differences which do not reach statistical significance must not be presented in such a way to mislead. Instances have occurred where claims have been based on published papers in which the arithmetic and/or statistical methodology was incorrect. Accordingly, before statistical information is included in promotional material it must have been subject to statistical appraisal." Ibid.

" 15.1 Representatives must be given adequate training and have sufficient scientific knowledge to enable them to provide full and accurate information about the medicines they promote.

15.2 Representatives must at all times maintain a high standard of ethical conduct in the discharge of their duties and must comply with all relevant requirements of the Code.

15.3 Representatives must not employ any inducement or subterfuge to gain an interview. No fee should be paid or offered for the grant of an interview.

15.4 Representatives must ensure that the frequency, timing and duration of calls on health professionals, administrative staff in hospitals and health authorities and the like together with the manner in which they are made, do not cause inconvenience. The wishes of the individuals on whom representatives wish to call and the arrangements in force at any particular establishment, must be observed."[707]

Another important clause if Clause 18, "Gifts and Inducements" and this has been breached 30 times:

" 18.1 No gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer or buy any medicine, subject to the provision of clause 18.2.

18.2 Gifts in the form of promotional aids and prizes whether related to a particular product or of general utility, may be distributed to members of the health professions and to appropriate administrative staff provided that the gift or prize is inexpensive and relevant to the practice of their profession or employment."[708]

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[707] Ibid p19.
[708] Ibid p23.

Further guidance has been given in the Code of Practice as to items of "general utility" which have been held to be acceptable gifts as they were inexpensive (something which has cost the pharmaceutical company no more that £5.00 excluding VAT) and of relevance to medical practice (e.g. pens, pads, diaries, nail brushes, surgical gloves, desk trays; calendars, a surgery security device, a low value phone card, a peak flow whistle, surgery scales, walking sticks and desk clocks).[709] Items which have been deemed unacceptable have included items for use in the home, (e.g. table mats), "irrelevant" items (e.g. plant seeds and compact discs) and expensive items (e.g. an x-ray light box and an age-sex register).[710]

Clause 19 gives guidance relating to "Hospitality and Meetings" and this clause has been breached 28 times:

> " 19.1 Companies are permitted to provide appropriate hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings, scientific congresses and other such meetings. Hospitality must be secondary to the purpose of the meeting. The level of hospitality offered must be appropriate and not out of proportion to the occasion and the costs involved must not exceed that level which the recipients would normally adopt when paying for themselves. It must not extend beyond members of health professions or appropriate administrative staff
>
> 19.2 Payments must not be made to doctors or groups of doctors, either directly or indirectly, for rental for rooms to be used for meetings.
>
> 19.3 When meetings are sponsored by pharmaceutical companies that fact must be disclosed in the papers relating to the meetings in any published proceedings."[711]

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[709] Ibid p24.
[710] Ibid.
[711] PMCPA (1997f)

Appendix XXVIII lists a selection of cases chosen by the Author, which were reported in 1996 and 1997 to the PMCPA and illustrate the types of case which the PMCPA are asked to investigate, the standard of conduct which constitutes a breach of the Code of Practice and the sort of promotional activities which are carried out in the UK.

When a company has breached the Code, the Chief Executive of the company involved must sign an undertaking to the effect that:

" all possible steps will be taken to avoid a similar breach of the Code."[712]

The company must also pay an administrative charge based on the number of matters ruled in breach of the Code. In more serious cases, the Board of Management of the ABPI may decide:

" • to reprimand the company and publish details of that reprimand;

• to require an audit of the company's procedures in relation to the Code to be carried out by the Prescription Medicines Code of Practice Authority and following that audit, decide whether to impose requirements on the company concerned to improve its procedures in relation to the Code;

• to require the company to publish a corrective statement;

• to suspend or expel the company from the ABPI; or

• in the case of companies not in membership of the ABPI, to remove the company from the list of non-member companies which have agreed to abide by the Code and to advise the Medicines Control Agency that responsibility for that company under the Code can no longer continue to be accepted." [713]

The producer of a documentary about promotional activities within the pharmaceutical industry, in the "First Tuesday" series, commented that these

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[712]Ibid p33.
[713]Ibid p34.

sanctions were inadequate and that self-policing was bound to be lax.[714] However, it is the opinion of the Author that the Code of Practice is operated very efficiently by the PMCPA and the Author would argue that the PMCPA is an excellent "watchdog" but that it is a watchdog without teeth in respect of controlling more serious breaches of the Code of Practice. It is suggested that use should be made of the more severe sanctions contained in the Regulations and companies should be fined for conducting unacceptable promotional activities. It remains to be seen whether or not the Licensing Authority will prosecute offences which are in breach of the Advertising Regulations, or if the cases will continue to be referred to the PMCPA.

4.10 Pharmacovigilance

4.10.1 The Yellow Card Scheme

Chapter Va of Directive 75/319/EEC sets out requirements in relation to pharmacovigilance, also known as postmarketing surveillance.[715] Article 29a states that:

> " In order to ensure the adoption of appropriate regulatory decisions concerning the medicinal products authorized within the Community, having regard to information obtained about adverse reactions to medicinal products under normal conditions of use, the Member States shall establish a pharmacovigilance system. This system shall be used to collect information useful in the surveillance of medicinal products, with particular reference to adverse reactions in human beings, and to evaluate such information scientifically.

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[714]Taylor (1991).
[715]The Commission has also published five draft guidelines relating to pharmacovigilance.

Such information shall be collated with data on consumption of medicinal products. This system shall also collate information on frequently observed misuse and serious abuse of medicinal products."

Article 29b sets out various definitions:

" 'adverse reaction' - means a reaction which is harmful and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function.

'serious adverse reaction' - means an adverse reaction which is fatal, life-threatening, disabling, incapacitating, or which results in or prolongs hospitalization.

'unexpected adverse reaction' - means an adverse reaction which is not mentioned in the summary of product characteristics.

'serious unexpected adverse reaction' - means an adverse reaction which is both serious and unexpected."

Article 29c requires that:

" The person responsible for placing the medicinal product on the market shall have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance.

That qualified person shall be responsible for the following:

(a) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the company, and to medical representatives, is collected and collated at a single point within the Community;

(b) the preparation for the competent authorities of the reports referred to in Article 29d, in such form as may be laid down by those authorities, in accordance with the relevant national or community guidelines;

(c) ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a medicinal product is answered fully and promptly,

including the provision of information about the volume of sales or prescriptions of the medicinal product concerned.

Article 29d states:

" The person responsible for placing the medicinal product on the market shall be required:

1. to record and to report all suspected serious adverse reactions which are brought to his attention by a health care professional to the competent authorities immediately, and in any case within 15 days of their receipt at the latest.
2. to maintain detailed records of all other suspected adverse reactions which are reported to him by a health care professional.

Unless other requirements have been laid down as a condition of the granting of authorization, these records shall be submitted to the competent authorities immediately upon request or at least every six months during the first two years following authorization, and once a year for the following three years. Thereafter the records shall be submitted at five-yearly intervals together with the application for renewal of the authorization, or immediately upon request. These records shall be accompanied by a scientific evaluation."

Article 29e states:

" The Member States shall take all appropriate measures to encourage doctors and other health care professionals to report suspected adverse reactions to the competent authorities.

The Member States may impose specific requirements on medical practitioners, in respect of the reporting of suspected serious or unexpected adverse reactions, in particular where such reporting is a condition of the authorization."

In the United Kingdom, adverse reactions to medicinal products are reported to the CSM on a voluntary basis by doctors, dentists, hospital pharmacists and HM

Coroners under the "Yellow Card scheme". Reports are also received from pharmaceutical companies as a condition of their licences. In Chapter One, Table 1 set out in a graph, the reports of adverse reactions to medicinal products which have been received by the CSM and its predecessor, the CSD. In relation to these reported adverse reactions, the CSM has issued advice on safety issues, in its annual reports, "Dear Doctor/Dentist/Pharmacist Letters", "Adverse Reaction Series Leaflets", "Current Problems" and "Current Problems in Pharmacovigilance".[716] The contents of these publications have been reviewed and Appendix XXIX lists the medicinal products which have been examined by the CSM.[717]

Despite the number of medicinal products which have been investigated by the CSM, it is acknowledged that adverse reactions to medicinal products are under-reported. In its annual report for 1994, the CSM commented:

> " The recent decrease in reporting has been of considerable concern to the Committee. It has reviewed, carefully, possible reasons for the decline and has introduced (with the Medicines Control Agency) a series of measures designed to reverse the trend. These include steps to promote the scheme, to facilitate reporting, and to ensure that ADR reporting is included in undergraduate and postgraduate medical training." [718]

This is not the first time that the CSM has taken measures to improve the reporting of adverse drug reactions. In 1983, the CSM established the Adverse Reactions Working Party with the following terms of reference:

> " To consider how best the Committee on Safety of Medicines should fulfil its statutory functions of promoting the collection and investigation of information relating to adverse reactions, for the purpose of enabling it to give advice on the

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[716]See Table 10, 11 and 12 for further details.
[717]Publications referenced under CSM and Medicines Commission et al.
[718]Medicines Commission et al (1995) p24.

> safety, quality or efficacy of medicinal products; and to make recommendations."
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The Working Party suggested that the need for post-marketing surveillance was illustrated by the fact that, prior to marketing, it was unlikely that there would be clinical information from more than 1000 - 2000 patients.[720] Table 31 shows that statistics require that large numbers of patients are exposed to a medicinal product to detect less common adverse reactions and, where there is a high background incidence of a disease, a larger number of patients require to be exposed to the medicinal product to determine the risk of that product causing the particular disease.

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[719]CSM (1985o). There was also an earlier report, CSM (1983h).
[720]Ibid.

Table 31 Number of Patients required to show a given increase in the incidence of adverse reactions.[721]

Incidence (risk) of ADR to be detected	Spontaneous background incidence of the adverse event	Minimum number of patients to be exposed.
1 in 100	0	360
	1 in 10,000	520
	1 in 1000	730
	1 in 100	2,000
1 in 500	0	1,800
	1 in 10,000	3,200
	1 in 1000	6,700
	1 in 100	35,900
1 in 1000	0	3,600
	1 in 10,000	7,300
	1 in 1000	20,300
	1 in 100	136,400
1 in 5000	0	18,200
	1 in 10,000	67,400
	1 in 1000	363,000
	1 in 100	3,225,000

The Working Party concluded that the numbers of patients participating in clinical trials should not be increased because:

" • exposure of large numbers of selected patients in carefully controlled clinical trials is not a substitute for safety experience obtained from normal clinical use.

• extended trials would delay the marketing of drugs and might deprive many patients of their potential benefits.

• the cost of greatly extended clinical trials would be large and would ultimately be borne by the community.

• there would be insufficient skilled scientific and medical staff to undertake the large number of trials required."[722]

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[721] Ibid.
[722] Ibid.

The Working Party outlined the functions of the Yellow Card scheme:

" • to draw attention to previously unsuspected possible adverse effects of drugs.
• to provide confirmatory evidence in the form of further reports of a particular problem following first alerts in the literature.
• to assist in the assessment of the risk/benefit ratio of a drug compared with other similar drugs." [723]

The Working Party stated that the advantages of a spontaneous reporting system are:

" • it begins to operate as soon as a drug is marketed;
• it relates to all drugs and patients;
• it is relatively inexpensive." [724]

and the disadvantages are:

• the reports are observations of suspected associations without data from an appropriate control group. There is an understandable tendency to report pharmacologically plausible ADRs which are temporarily related to exposure.
• under-reporting occurs. The amount of under-reporting is unknown and probably varies depending on the nature of the drug and the reaction.
• doctors sometimes delay submitting reports.
• reports can be inaccurate or imprecise.
• where there is publicity about a problem with a particular drug, the reporting rate for that drug usually rises. This bias is an important factor in reducing the value of yellow cards in comparing the safety of different drugs.
• there is often uncertainty about the number of patients who have been exposed since this has to be estimated from an analysis of prescription data and the analysis is complicated by repeat prescriptions and differences in quantities and doses prescribed.

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[723] Ibid.
[724] Ibid.

- it may be difficult to compare ADRs produced by different drugs in the same therapeutic group because the drugs may be used in different types of patients." [725]

The Working Party analysed other postmarketing surveillance techniques including cohort studies, case control studies, record linkage and the use of statistics from the Office of Population Censuses and Surveys. It was concluded that:

" There is no immediate prospect of improvements to the monitoring of rare or long-latency ADRs. In the long-term, record linkage systems might help and we recommend that current research into the technique in the UK should be maintained." [726]

The Working Party also recommended that pharmaceutical companies should undertake postmarketing surveillance studies on newly marketed products, which were intended for long-term use.

Following a recommendation of the Working Party,[727] the following important advice to doctors regarding the reporting of adverse reactions to drugs appears in the British National Formulary:

" Suspected adverse reactions to *any* therapeutic agent should be reported, including drugs (those taken for *self-medication* as well as those prescribed), blood products, vaccines, X-ray contrast media, dental or surgical materials, intra-uterine devices, and contact lens fluids.

ADROIT. Adverse drug reactions On-Line Information Tracking (ADROIT) has now been introduced to facilitate the monitoring of adverse drug reactions.

NEWER DRUGS. These are indicated by the sign ▼. Doctors are asked to report *all* suspected reactions (i.e. any adverse or any unexpected event, however minor, which could conceivably be attributed to the drug). Reports should be

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[725] Ibid.
[726] Ibid.
[727] CSM (1983h).

made despite uncertainty about a causal relationship, irrespective of whether the reaction is well recognised, and even if other drugs have been given concurrently.

ESTABLISHED DRUGS. Doctors are asked to report *all* serious suspected reactions, including those that are fatal, life-threatening, disabling, incapacitating, or which result in or prolong hospitalisation; they should be reported even if the effect is well recognised. Examples include anaphylaxis, blood disorders, endocrine disturbances, effects on fertility, haemorrhage from any site, renal impairment, jaundice, ophthalmic disorders, severe CNS effects, severe skin reactions, reactions in pregnant women and any drug interactions. Reports of serious adverse reactions are required to enable risk/benefit ratios to be compared with other drugs of a similar class. For established drugs, doctors are asked not to report well-known, relatively minor side-effects, such as dry mouth with tricyclic antidepressants, constipation with opioid, or nausea with digoxin.

Special Problems

Delayed Drug Effects. Some reactions (e.g. cancers, chloroquine retinopathy, and retroperitoneal fibrosis) may become manifest months or years after exposure. Any suspicion of such an association should be reported.

The elderly. Doctors are asked to be particularly alert to adverse reactions in the elderly.

Congenital Abnormalities. When an infant is born with a congenital abnormality or there is a malformed aborted fetus doctors are asked to consider whether this might be an adverse reaction to a drug and to report all drugs (including self-medication) taken during pregnancy.

Vaccines. Doctors are asked to report all suspected reactions to both new and established vaccines. The balance between risks and benefits needs to be kept under continuous review."[728]

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[728] BMA and Royal Pharmaceutical Society (1997) p10.

Table 32 lists the medicinal products which have ▼ status.

Table 32 New Medicinal Products with ▼ Status (1997).

Abelcet (Amphotericin); Accusite Injectable Gel (Fluorouracil/Adrenaline); ACT-IIIB DTP (DTP IIIB conjugate); Acular (Ketorolac trometamol); Adifax (Dexfenfluramine); Airomir (Salbutamol); Alphagan (Brimonidine); Amaryl (Glimepiride); Andropatch (Testosterone); Aricept (Donepezil); Arimidex (Anastrozole); Avaxim (Hepatitis A virus inactivated); Avonex (Interferon beta-1a); Betaferon (Interferon beta-1b); Botox (Botulinum toxin); Cabaser (Cabergoline); Caelyx (Doxorubicin); Calcort (Deflazacort); Campral EC (Acamprosate); Campto (Irinotecan) ; Casodex (Bicalutamide); Cefrom (Cefpirome); Cellcept (Mycophenolate mofetil); Cipramil (Citalopram); Clotam (Tolfenamic acid); Cozaar (Losartan); Cozaar-Comp (Losartan & Hydrochlorothiazide); Creon 25000 (Pancreatin); Crixivan (Indinavir) ; Curatoderm (Tacalcitol); Daunoxome (Daunorubicin); De-Capeptyl SR (Triptorelin); Differin (Adapalene); Diovan (Valsartan); Dipeptiven (N (2)-L-Alanyl-L-Glutamine); Dostinex (Cabergoline); Dotarem (Gadoteric acid); Dutonin (Nefazodone); Echovist (Galactose); Edronax (Reboxetine); Efexor (Venlafaxine); Endorem (Ferumoxides); Epivir (Lamivudine); Erecnos (Thymoxamine); Ethmozine (Moracizine); Ethyol (Amifostine); Fareston (Toremifene); Femara (Letrozole); Flomax (Tamsulosin); Foradil (Eformoterol; Fosamax (Alendronate; Gemzar (Gemcitabine); Glucagen GE (Glucagon rys); Gonal-F (Follitropin alfa); Granocyte (Lenograstim); Hexalen (Altretamine); Hivid (Zalcitabine); Humalog (Insulin lispro); Hycamtin (Topotecan); Ikorel (Nicorandil); Innohep 20000 (Tinzaparin); Invirase (Saquinavir); Lamictal (Lamotrigine); Lescol (Fluvastatin); Leucomax (molgramostim); Leustat (Cladribine) ; Levovist (Galactose & Palmitic Acid); Lipitor (Atorvastatin); Lipobay (Cerivastatin); Livostin (Levocabastine); Manerix (Moclobemide) ; Mifegyne (Mifepristone); Mirena (Levonorgestrel); Mobic (Meloxicam); Naramig (Naratriptan); Naropin (Ropivacaine); Nasacort (Triamcinolone acetonide); Nasonex (Mometasone); Navelbine (Vinorelbine); NeoRecormon (Epoetin beta (rch)); Neupogen (Filgrastim); Neurontin (Gabapentin); Neutrexin (Trimetrexate); Nimbex (Cisatracurium); Nipent (Pentostatin); Nootropil (Piracetam); Norplant (Levonorgestrel); Norvir (Ritonavir); Novoseven (Eptacog alfa); Nutrizym 22 (Pancreatin); Octreoscan (Pentretreotide); Optimax (L-Trytophan); Pancrease HL (Pancreatin); Perdix (Moexipril); Physiotens (Moxonidine); Preservex Aceclofenac); Propess-RS (Dinoprostone); Protium (Pantoprazole); Pulmozyme (Dorsonase alfa); Puregon (Follitropin beta); Pylorid (Ranitidine bismuth citrate); Rapilysin (Reteplase); ReoPro (Abciximab); Requip (Ropinirole); Rilutek (Riluzole); Rocephin (Ceftriaxone); Serdolect (Sertindole); Seroquel (Quetiapine); Sevoflurane (Sevoflurane); Skelid (Tiludronate sodium); Syscor MR (Nisoldipine); Taxol (Paclitaxel); Taxotere (Docetaxel); Technescan MAG3 (Betiatide); Telfast (Fexofenadine); Timoptol LA (Timolol); Tomudex (Raltitrexed); Topamax (Topiramate); Tramake (Tramadol); Trivax-IIIB (DTP-IIIB conjugate); Trusopt (Dorzolamide); Twinrix (Hepatitis A (inactivated) and rDNA Hepatitis B); Ultiva (Remifentanil); Valtrex (Valaciclovir); Vectavir (Penciclovir); Vesanoid (Tretinoin); Visipaque (Iodixanol); Vistide (Cidofovir); Wellvone (Atovaquone); Xalatan (Latanoprost); Xatral (Alfuzosin); Zamadol (Tramadol); Zerit (Stavudine); Zispin (Mirtazapine); Zomig (Zolmitriptan); Zorac (Tazarotene); Zydol (Tramadol); and Zyprexa (Olanzapine).

In 1992, a pilot scheme to enable hospital pharmacists to report adverse reactions was introduced in the Northern Region.

> " The results continue to be encouraging and the Committee will be considering these, as well as their wider implications, when the full details of the pilot scheme are available." [729]

A study by Wolfson et al concerning adverse reactions reporting by community pharmacists concluded:

> " This research suggests that reporting of information on ADRs by community pharmacists to the CSM is feasible, and would be of value to the CSM." [730]

However, despite these various improvements, the CSM and MCA again acknowledged in 1997, that many adverse reactions were not still not being reported and further stated that there had been a fall in the number of reports received:

> " The MCA/CSM are seeking ways to stimulate the reporting of serious reactions. There is a need also to cover those medicines increasingly being made available to patients without prescription through pharmacies.
>
> Recent research in the UK and international experience suggest that pharmacists can provide a useful contribution to ADR reporting. In particular studies have shown that hospital pharmacists can be useful in enhancing reporting from hospitals, which are an important source of serious ADRs. Although the role of community pharmacists is less clear it is likely that they can play a role in areas where there is virtually no reporting by doctors e.g. for over the counter and unlicensed medicinal (herbal) products."[731]

From April 1997, all hospital pharmacists can report adverse reactions via the Yellow Card Scheme and a "demonstration" scheme has been introduced for community pharmacists in four areas.[732] However, a recent Editorial in the Pharmaceutical Journal expressed frustration with these proposals:

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[729]Medicines Commission et al (1994) p24.
[730]Wolfson et al (1993a) and (1993b).
[731] MCA (1996i) p2. The MCA issued MLX229 as part of the consultation process.
[732] MCA/CSM (1997a).

> " The many years of procrastination on the part of the medicines regulatory system is now at an end. Thus pharmacists will now be able to play a recognised part in the officially established procedure for protecting public health in this field. We use the phrase 'a part' deliberately, because pharmacists as yet will not be participating fully in adverse drug reaction reporting. While hospital pharmacists will be engaged on a national basis, community pharmacists will only be reporting on a trial basis in four locations, and even then they will be asked to focus on areas where there is limited reporting by doctors, such as over-the-counter medicines and herbal products. We have described this approach as half-baked, but, in the light of years of intransigence, welcomed it as better than nothing. We feel sure that community pharmacists in the chosen localities will respond with a will."[733]

In the opinion of the Author, the Yellow Card Scheme should be extended immediately to include all community pharmacists, as this could possibly reverse the trend of the under-reporting of adverse reactions, particularly as there are many former prescription only products which are now available over-the-counter from pharmacies.[734] As a further means of encouraging the reporting of adverse reactions, it is suggested by the Author that, in the future, the possibility of limited reporting by patients should be considered, as was discussed in recent study conducted in the Netherlands:

> " Our findings show that reporting by patients may contribute to earlier detection of known and unknown adverse drug reactions. The information available from patients in the telephone service was, however, often crude and incomplete in comparison with professional adverse rug reaction reports. Therefore, the telephone service cannot be relied on as an independent reporting system; it might generate too many false alarms. A combination of information from patients and health care professionals might, however, enable earlier detection. Additional

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[733] Pharm J (1997g).

information is relevant because alerts are often based on only a few reports but too high demands on quality of the reports may impair their capacity for early warning. We suggest that patient reporting may play an additional role in pharmacovigilance."[735]

4.10.2 Withdrawals and Variations

Once an adverse reaction has been identified, the following may occur:

- there may be no action as it is a well-recognised adverse reaction and the risks of continuing to use the medicinal product do not outweigh the benefits;

- there may be a report in the medical literature or Current Problems in Pharmacovigilance and medicinal product may be asked to be more closely monitored by health professionals;

- there may be a variation to the product licence/marketing authorisation (warning strengthened in product literature, use controlled etc.);

- the Health Ministers may issue a Section 62 Order which prohibits the sale, supply or importation of the specified medicinal product, where deemed necessary to do so in the interests of safety;[736]

- the medicinal product may be withdrawn voluntarily from the market; or

- the product licence/marketing authorisation may be revoked.

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[734] As discussed .
[735] Egberts et al (1996) p531.
[736] This procedure has been used on several occasions. For example, Bal Jivan Chamcho (1976/1861), Phenacetin (1974/1082), Hexachlorophane (1973/1120) and Chloroform(1979/382). These Orders have been revoked or renewed, and details can be found in Appendix II.

Professor Asscher, a past Chairman of the CSM commented:

> " It is a common misconception that the CSM uses these data to banish drugs. On most occasions the information is used to fine tune drug prescribing after licensing with the full collaboration of the industry. By far and away the commonest outcome of our deliberations on ADR data is to suggest alterations in the data sheets which the company then communicates to prescribers. Revocations of licences are rare and, as in the case of the granting of the licence, these decisions are based on a risk-benefit analysis. In reaching advice to recommend revocation, the members of the CSM are well aware of the many factors that may exaggerate risk and that restriction of the licence to treatment of certain patient groups may be preferable to revocation. A good example of this was the restriction of the use of phenylbutazone to patients with ankylosing spondylitis. Revocation decisions are never universally approved of. Some will say 'why were so many patients harmed before CSM took action?', whereas others will say 'how dare the CSM deprive us of this useful drug.'".[737]

Appendix XXX lists some recent examples of where the CSM has suggested that a variation is made to some aspect of the use of a medicinal product. This Appendix lists the medicinal product involved alongside the adverse reactions reported and the suggested variation to the product's use

As stated above, medicinal products may also be withdrawn for safety reasons or have their product licence/marketing authorisation revoked. Several authors have encountered difficulties in identifying safety withdrawals.

> " Identification of safety issues surrounding drug products is difficult because the severity of safety problems can vary greatly; publicity about such problems is not always proportional to the significance of the problem, and sometimes safety concerns tend to be controversial."[738]

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[737] Asscher (1990).
[738] Hass et al. (1985) p237

Bakke et al discussed the problems in defining "withdrawal" and "safety reasons":

> " When a drug ceases to be marketed, it is often difficult to determine whether it has been "withdrawn" (or the licence simply allowed to lapse) by the manufacturer or "removed" by the regulatory agency. Such an action is usually a combination of both, and infinite gradations and combinations are possible. In addition, there are "recalls", usually caused by technical problems with a particular batch, but inherent problems with the method of manufacture may occasionally result in permanent withdrawal of a product (e.g.. polidexide). [...] It was often particularly difficult to determine whether a drug was "discontinued for a safety reason". The question of safety was usually inseparable from that of the drug's efficacy for its intended use, and often the question of commercial viability was involved as well."[739]

Bakke et al. also commented on the lack of published lists of safety withdrawals in both the United Kingdom and the United States. Medawar suggested that:

> " In the UK, the authorities do not explain themselves, and prefer not to. This is especially true when more sensitive issues are involved - as anything to do with drug safety always is. Secrecy means not explaining things, and sometimes refusing to even discuss them."[740]

Appendix XXXI lists medicinal products which have been withdrawn for safety reasons either voluntarily or compulsorily, since Thalidomide was withdrawn. The information used in this table is taken from the Committee on Safety of Medicines' publications listed in Appendix VIII, the BNF and "Drug Discovery: The Evolution of Modern Medicines".[741]

The Author suggests that, wherever possible, medicinal products should not have their product licence/marketing authorisation revoked, as there will always be some

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[739]Bakke et al. (1984) p560-561
[740] Medawar (1992) p244.

patients who have responded well to the particular medicinal product and there is not a substitute product to help them. Thalidomide is an excellent example of a medicinal product which has very great risks but, as discussed in Chapter One, has been found to be extremely useful in the treatment of various serious diseases.[742] It was stated earlier in this chapter[743] that Thalidomide is available as an unlicensed medicinal product. In the opinion of the Author, more control could be exercised if products such as Thalidomide were licensed but under very strict conditions. For example, Isotretinoin (Roaccutane) manufactured by Roche (and used in the treatment of cystic and conglobate acne) is teratogenic. However, it was granted a product licence in 1982:

> " It was realised that the drug was teratogenic and a licence was granted only because of its exceptional efficacy in patients at risk of physical or psychological scarring from intractable acne. Effective contraception is essential for women on this drug and, to ensure that this remained effective, CSM obtained evidence that Roaccutane does not interfere with the action of the oral contraceptive pill. Because of the potential hazard of the treatment the drug is intended for use only under the closest supervision. To this end the promotion of the drug is limited to consultant dermatologists, its supply to hospital pharmacists, and it is licensed only for 'Cystic and conglobate acne and severe acne which has failed to respond to an adequate course of a systemic anti-microbial agent'. In the USA, where the drug is more widely available and has been given at higher doses than in the UK, a number of fetal abnormalities are being reported in women who took this drug when not protected against pregnancy, confirming it as a major human teratogen. The abnormalities include hydrocephalus and microcephaly. There have been no cases reported in the UK. This therefore seems an appropriate time to alert all practitioners to the drug's potential hazards in order that the very strict precautions regarding its use may be re-inforced. For example, it has been found

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[741] Sneader (1985).
[742] p4.

> in the USA that treatment has been so effective for some patients that there was a tendency for repeat prescriptions to be passed on for use by a friend. Thus all doctors should be aware of these hazards."[744]

Therefore, it is possible to license even the most potentially "dangerous" medicinal products and use them with an acceptable risks/benefit ratio by communicating the risks to health professionals and patients, in CSM publications and in product literature.

The CSM currently communicates information regarding adverse reactions to health professionals via the Current Problems in Pharmacovigilance series and Dear Doctor Letters. Professor Asscher has stated that:

> " The objective must be to convey our message to the Profession before it reaches the patients. At times we have failed because of leaks to the media, the vagaries of mailing companies or the postal services. This problem might be overcome with the advent of Medical Television programmes as these could convey urgent messages to doctors. In all of our communications, the CSM must recall the dictum that it is not only what you say but also how you say it. The difficulty here is to satisfy all of the parties involved: the patients, the profession, the industry, not forgetting the legal profession."[745]

In 1995, the way in which information regarding the safety of certain types of oral contraceptives was conveyed to health professionals and the public was heavily criticised. This led to a "pill scare" among patients and a rise in abortions was reported by the British Pregnancy Advisory Service.[746]

As was stated earlier by the Author with regard to information supplied to patients, transparency relating to the way in which decisions on adverse reactions are

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[743] p196.
[744] CSM (1983g).
[745] Asscher (1990).

made should be encouraged, and as much information as possible should be supplied to patients about adverse reactions to medicinal products.

4.11 Conclusions

The difficulty experienced by the Author was in determining the true extent of any threat to consumer safety posed by ineffective control of medicinal products by the legislative framework. In 1993, the MCA published a book "Towards Safe Medicines", which featured a question and answer section. In relation to the question "Could there ever be another thalidomide type disaster?", the MCA stated:

> " Although no absolute guarantee can be given, the chances of this happening again are very remote. This is because of the measures now taken by regulatory authorities to test all new formulations of active substances before they are allowed on to the market and to monitor for unexpected and unacceptable side effects once marketed. However, a categorical *No* cannot be given to this question since we cannot be sure that such a thing would never happen again."

The Author has stated on several occasions that no medicinal product is completely safe. Therefore, the function of legislation must be to lessen the risks of medicinal products causing harm to consumers. However, there may well be situations in the future which could not have been anticipated by legislation. It is suggested by the Author that an example of such a situation was the contamination of blood products with HIV.

In relation to the operation of the legislative framework, the Author concluded that: the regulatory schemes controlling medical devices and homeopathic products should be monitored; exempted herbal products should be brought within the control

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[746] Pharmaceutical Journal (1996c).

of the legisaltive framework; unlicensed medicinal products supplied on a named patient basis should also be brought under the control of the legislative framework; potential conflicts of interest within regulatory bodies should be monitored; switches in the legal status of medicinal products should be accompanied by more information to the patient, stonger sanctions for pharmacists who do not supervise the supply of pharmacy medicines and ADR reporting by community pharmacists; more information should be made available to patients about medicinal products and the process by which the legislative framework operates; undesirable promotional practices should be controlled by the legislative framework not left to self-regulation alone; and, ADRs are under-reported and community pharmacists should be allowed to report adverse reactions.

Part III

The Impact of the Legislative Framework on Legal Redress

4.12 Introduction

Most discussions involving issues of legal redress regarding medical negligence or product liability relating to medicinal products inevitably centre on proposals for a no-fault compensation scheme such as is operated in New Zealand[747] or an insurance scheme such as is operated in countries such as Sweden, Finland and Japan.[748] For example, in 1993, a group of MPs tabled an early day motion calling for a change in the law relating to side effects from steroids.

> " That this House expresses its serious concern about the number of patients who are forced to seek redress via the judicial system after suffering the side-effects of long term steroid treatment; believes that a no fault compensation scheme would be preferable to protracted legal action; and calls on the Government to investigate the establishment of such a scheme, with help from the

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[747] Shulman and Lasagna (1990), Smith (1982a), (1982b) and (1982c), McLean (1977) and Diamond and Laurence (1985).
[748] M. Brahams (1988a), (1988b), (1988c), D. Brahams (1988l), McGregor Vennell (1989), Oldertz (1984), Howells (1990b) and (1991b), and Katahira and Satoh (1990).

> pharmaceutical industry, to improve and protect the quality of lives for patients."[749]

In 1994, the Legal Aid Board discussed the possible introduction of a Drug Compensation Tribunal which had statutory powers to "investigate alleged harmful medicinal products and order compensation to those who had been injured".[750] It was suggested that the Tribunal could have the following features:

> " (i) The tribunal would be primarily medical but perhaps with a legal chairman. It would have to be independent of the drug manufacturers, or at least any member nominated by the industry would have to be balanced by a member nominated by consumer groups.
>
> (ii) Individuals alleging that they had been harmed by drugs or given inadequate warnings would complete an application to the tribunal for compensation specifying basic details of the drugs used, period taken and alleged harmful effects.
>
> (iii) The tribunal would decide based on applications received whether a certain drug required investigation. If so, it would call upon the drug manufacturer to respond to the complaints made.
>
> (iv) Where necessary the tribunal would commission its own research into the drug and obtain whatever medical or legal assistance it required.
>
> (v) The tribunal would have power to order disclosure of research and documents from the manufacturer at any stage, subject to suitable safeguards.
>
> (vi) Ultimately the tribunal would come to a determination as to whether any drug was harmful and whether the manufacturer had adequately warned of its side effects.

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[749]Early Day Motion No. 2346. Also see Pharmaceutical Journal (1993aa).
[750] Legal Aid Board (1994).

> (vii) Where fault was found, the tribunal would order a compensation scheme to be set up and would set up a system for investigating and paying compensation to individual applicants."[751]

However, the Legal Aid Board conceded that the existence of such a Tribunal raised as many questions as it answered, particularly in relation to funding and how this new scheme would fit into existing legislation.

Such discussions, although of general interest, are not of relevance to the development of an alternative scheme of compensation in respect of product liability in Europe. It is argued by the Author that the current system of product liability will not be set aside in favour of an alternative scheme owing to the extensive discussions, conducted at UK and European level which excluded the proposal that medicinal products should be treated separately from other products(as discussed in Chapter 3), and which eventually culminated in the 1985 Directive and the enactment of the Consumer Protection Act 1987. For example, the Pearson Commission concluded:

> " It has been made clear to us that the pharmaceutical industry is opposed to strict liability. We acknowledge the force of these arguments, and we recognise that the difficulties faced by drug manufacturers would if anything be aggravated by the imposition of strict liability. We have nevertheless concluded that no special treatment could be justified. The demand for fuller and surer compensation for injuries caused by drugs is now an international phenomenon. The context is one in which the industry finds itself under pressure, whatever its legal liabilities in any one country. These difficulties, and the more fundamental problem of trying to produce safe drugs would not be solved by avoiding a change to strict liability in the United Kingdom."[752]

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[751] Ibid p26.
[752] Pearson (1978a) p273.

However, interestingly, two alternative compensation schemes relating to medicinal products operate in the UK: the vaccine damage payments scheme and the clinical trial compensation scheme. This demonstrates that there is a precedent for treating medicinal products differently to other types of product. Could it be possible, therefore, for medicinal products to be exempt from the provisions of the Consumer Protection Act 1987?

In 1978, the Royal Commission on Civil Liability and Compensation for Personal Injury (Pearson Commission) considered the issue of vaccine damage and concluded:

> " We think that the basis of liability should not be fault but should be strict, that is to say that, where a plaintiff can show on the balance of probabilities that the injury suffered was attributable to the administration of a vaccine on the recommendation of the Government or a local authority, he should be entitled to compensation. Subject to these matters of causation and fact, there should be no defences. We reach these conclusions because vaccination is recommended by the state for the benefit of the community; and where it causes injury the state ought to provide compensation, as part of the cost of providing protection for the community as a whole.
>
> We are conscious of the view that special compensation provision for vaccine damage might act as a deterrent to vaccination, on the grounds that it would imply that there must be real danger. But there is also the opposite view which we share, that the Government must be confident about vaccination before it would make such a provision. We naturally hope that any increase in litigation resulting from our recommendations, and any attendant publicity, will not have an adverse impact on the future vaccination programme."[753]

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[753] Pearson (1978a) p298.

In 1979, the Vaccine Damage Payments Act was enacted.[754] In 1994, Ferguson undertook a review of the vaccine damage compensation scheme and commented that the drawbacks of the scheme were that the maximum lump sum payment available under the Scheme is £30,000 (lower than the amount of damages which would be expected to be awarded by the Courts) and that claimants require to show that they have suffered "severe disability", which Ferguson explained has been defined as being 80 per cent disability.[755] From 1989 to 1993, there were nine cases heard by the Vaccine Damage Tribunal in Scotland; three were successful.[756] Ferguson concluded as follows:

> " Given the lack of consensus among members of the medical profession and the continuing disagreement within the scientific community as to whether pertussis is capable of causing brain damage, it is hardly surprising that the courts have encountered great difficulty in determining cases of alleged vaccine injury. It is submitted that it will be no less problematic for persons claiming under the compensation scheme established by the 1979 Act to prove that their injuries were *caused* be vaccination. In addition, the 1979 Act, the "80 per cent disability" requirement presents a formidable hurdle for many claimants. In short, even in cases in which the relevant medical records have been preserved, persons who pursue compensation for alleged vaccine damage face an uphill struggle."[757]

The Association of the British Pharmaceutical Industry produced clinical trial compensation guidelines in 1991 replacing an earlier scheme which had operated since 1983.[758] As a preamble to these guidelines, the ABPI commented that it favoured:

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[754] For general background and discussion see Teff (1977), Brahams (1985) and Gamble (1979).
[755] Ferguson (1994).
[756] Parker (1994)
[757] Ferguson (1994) p82.
[758] ABPI (1991). For general background and discussion see Hodges (1991), Lancet (1980b), Gillon (1992), Tunkel (1989), Ciba Foundation Study Group (1980), and Diamond and Laurence (1983).

" a simple and expedited procedure in relation to the provision of compensation for injury caused by participation in clinical trials. The Association therefore recommends that a member company sponsoring a clinical trial should provide without legal commitment a written assurance to the investigator - and through him to the relevant research ethics committee - that the following Guidelines will be adhered to in the event of injury caused to a patient attributable to participation in the trial in question."[759]

The basic principles of these Guidelines are as follows:

" 1.1 Notwithstanding the absence of legal commitment, the company should pay compensation to patient-volunteers suffering bodily injury (including death) in accordance with these Guidelines.

1.2 Compensation should be paid when, on the balance of probabilities, the injury was attributable to the administration of a medicinal product under trial or any clinical intervention or procedure provided for by the protocol that would not have occurred but for the inclusion of the patient in the trial.

1.3 Compensation should be paid to a child injured in utero through the participation of the subject's mother in a clinical trial as if the child were a patient-volunteer with the full benefit of these Guidelines.

1.4 Compensation should only be paid for the more serious injury of an enduring and disabling character (including exacerbation of an existing condition) and not for temporary pain or discomfort or less serious or curable complaints.

1.5 Where there is an adverse reaction to a medicinal product under trial and injury is caused by a procedure adopted to deal with that adverse reaction, compensation should be paid for such injury as if it were caused directly by the medicinal product under trial.

1.6 Neither the fact that the adverse reaction causing the injury was foreseeable or predictable, nor the fact that the patient has freely consented (whether in writing or otherwise) to participate in the trial should exclude a patient from

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[759] Ibid

consideration for compensation under these Guidelines, although compensation may be abated or excluded.

1.7 For the avoidance of doubt, compensation should be paid regardless of whether the patient is able to prove that the company has been negligent in relation to research or development of the medicinal product under trial or that the product is defective and therefore, as the producer, the company is subject to strict liability in respect of injuries caused by it."[760]

It is stated in the Guidelines that the amount of compensation should be consistent with the quantum of damages awarded for similar injuries by the English courts.[761] Hodges reviewed these guidelines and commented that the approach taken by the ABPI was "a logical application of legal principles". He further commented that research injuries were extremely rare: no examples were given of instances when the provisions in the guidelines were utilised.[762]

Both the vaccine damage compensation scheme and the clinical trial compensation scheme are optional, and a patient always has the option of pursuing a claim in terms of the Consumer Protection Act 1987 or by way of a negligence action whichever is applicable. In England, a group of parents of allegedly vaccine-damaged children has decided to launch a number of test cases in the English courts seeking to prove that batches of vaccine were defective.[763]

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[760] Ibid. The limitations on compensation are as follows:
3.1 No compensation should be paid for the failure of a medicinal product to have its intended effect or to provide any other benefit to the patient.
3.2 No compensation should be paid for injury caused by other licensed medicinal products administered to the patient for the purpose of comparison with the product under trial.
3.3 No compensation should be paid to patients receiving placebo in consideration of its failure to provide a therapeutic benefit.
3.4 No compensation should be paid (or it should be abated as the case may be) to the extent that the injury has arisen:
3.4.1 through a significant departure from the agreed protocol;
3.4.2 through the wrongful act or default of a third party, including a doctor's failure to deal adequately with an adverse reaction;
3.4.3 through contributory negligence by the patient.

[761] Ibid.

[762] Hodges (1991).

[763] Liability, Risks and Insurance. (1997).

It is suggested by the Author that neither of these schemes or any other form of compensation scheme such as that suggested by the Legal Aid Board or the scheme relating to side effects of steroids could form the basis of a viable replacement scheme for medicinal products in place of the Consumer Protection Act 1987. Another alternative is that the Government has instituted its own compensation scheme in relation to HIV-contaminated blood and blood products, and contaminated human growth hormone. It is suggested by the Author that these Government schemes were instituted because these products were not subject to any control under the Medicines Act 1968. In any event, as discussed earlier, there is no likelihood of the Consumer Protection Act 1987 being replaced, in the medium term, by a no fault compensation scheme such as the scheme operated in New Zealand mentioned earlier or medicinal products being exempted from its provisions. However, what also must be borne in mind, is that the Consumer Protection Act did not remove a consumer's right to pursue a negligence action in respect of an alleged defective product. For example, negligence actions require to be pursued for products put into circulation prior to the Consumer Protection Act 1987 coming into force in 1988, and there may be alleged defective products which fall outwith the Act.

The problem is that it is difficult to assess how "successful" the Consumer Protection Act 1987 will be in relation to providing legal redress relating to medicinal products as, although the Act has been in effect since 1 March 1988, there have been no reported cases under the Act involving medicinal products. Recently, the National Consumer Council published an analysis of the Act entitled, "Unsafe

Products. How the Consumer Protection Act Works for Consumers".[764] In this report, it was stated:

> " At the time Part I of the Act was brought into force, the National Consumer Council hoped that one of the key benefits of the Act would be to give consumers increased awareness of their entitlement to compensation if injured by defective products. We hoped that if consumers were able to gain recompense for injury caused by faulty goods more easily manufacturers would have an incentive to improve the safety of their products.
>
> The insurance industry said that it expected premiums to increase to compensate for an increase in low-value claims, the kind of claims consumers might pursue by themselves, but that it would not have a dramatic effect on premiums. It did not see the Act as increasing the legal rights of consumers significantly.
>
> We had concerns about the Act, notably the inclusion of the 'development risk defence' and the exclusion of primary agricultural products. [...]
>
> Few of our hopes or our fears have been realised. Consumers do not appear to be using the Act in low or high value claims in any large numbers. It does not appear that there has been a reduction in the number of unsafe goods reported, although it is hard to compare like with like. Accidents in the home have not decreased. On the other hand, because so few cases have been brought, the strength of the development risk defence has not been tried. Equally we do not know whether the exemption for primary agricultural products has prevented a consumer claiming compensation form a farmer for, for example, food poisoning." [765]

Despite the lack of reported cases, it is clear that the most controversial aspect of the Consumer Protection Act 1987, in relation to medicinal products, is the development risks defence. This will be discussed in the next section.

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[764] NCC (1995).
[765] Ibid pp2-3.

4.13 The Development Risks Defence

The report of the Law Commissions, the report of the Pearson Commission, the Strasbourg Convention and earlier drafts of the Directive on liability for defective products did not include a development risks defence. The Pearson Commission stated:

> " A dangerous 'design defect' has a greater potential than a 'manufacturing defect' for widespread injuries caused by a single product range. The risks involved particularly affect industries which produce potentially dangerous products, such as chemicals, drugs, aircraft and motor cars and the more so where these are subject to continuous technological improvements. It is important to such industries to consider whether there should be carried over into a system of strict liability something parallel to the "state of the art" defence available under the present system of liability in negligence. The production of a new drug is a striking example of the kind of development risk which might be covered by such a defence.
>
> It can be argued that to hold the producer liable in such cases would be to impose on him - and through him, on the product's consumers as a whole - a responsibility for compensating injuries even when it might have been impossible to prevent the defect occurring. It is further argued that this responsibility, and the cost of insuring against the risks involved, might severely deter the development of new products, particularly those small developments which might lead cumulatively to a major advance; and that this is sufficiently contrary to the interests of consumers themselves to outweigh the case for tort compensation, at least through the medium of strict liability. On the other hand, to exclude development risks from a regime of strict liability would be to leave a gap in the compensation cover, through which, for example, the victims of another

thalidomide disaster might easily slip. We recommend that the producer should not be allowed a defence of development risk." [766]

However, as explained in Chapter 3, the Directive on liability for defective products included a development risks defence. The Department of Trade And Industry (DTI) discussed the inclusion of this defence:

" A true development risk is rare and yet the availability of the defence has been one of the most controversial issues raised by the Directive. Some have argued that the inclusion of such a defence would leave a significant gap in the liability system through which victims of unforeseeable disasters would remain uncompensated and which could bring back many of the complexities and legal arguments that the introduction of strict liability is supposed to avoid. Manufacturers, on the other hand, have argued that it would be wrong in principle, and disastrous in practice, for businesses to be held liable for defects that they could not possibly have foreseen. They believe that the absence of this defence would raise insurance costs and inhibit innovation, especially in high risk industries. Many useful new products, which might entail a development risk, would not be put on the market, and consumers as well as business would lose out.

The Government have therefore accepted that there are grounds for the defence in the UK given that it is stringently defined in the Directive. It is understood that the defence should be interpreted as meaning that the producer will not be liable if he proves that, given the state of scientific and technical knowledge at the time the product was put into circulation, no producer of a product of that kind could have been expected to have discovered the existence of the defect. The burden of proof will fall squarely on the producer to show that the defect could not reasonably be expected to be discovered. It will not necessarily be enough to show that he has done as many tests as his competitor, nor that he did all the tests required of him by a government regulation setting a minimum standard. It will

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[766]Pearson (1978a) p269.

> therefore not be easy for a producer successfully to plead this defence, but it should be remembered that the basis of liability under the Directive, on which all claims must rest, is that the product did not provide the safety which is reasonably to be expected of it, given the time it was put into circulation." [767]

Clark commented that prior to the implementation of the Consumer Protection Act:

> " Much of the time spent on debating the proposed new strict liability regime concerned development risks. Discussion of the issue was prolonged and at times passionate. The European Commission and the European Parliament were divided on this question, reflecting the views of the Member States. [...] Put simply, those against the defence argue that its inclusion emasculates strict liability and subverts the policy aims underlying the new regime. The opposing view is that without such a defence, potential liability would be indeterminate and could be catastrophic, and that more cogent policy considerations (including the wish not to stifle innovation) outweighed the aims of the purists." [768]

Clark further discussed how the wording of the development risks defence used in the Consumer Protection Act is substantially different from the wording used in the Directive. Article 7(e) of the Directive states:

> " that the state of scientific and technical knowledge at the time when he put the product into circulation was not such as to enable the existence of the defect to be discovered"

Section 4(1)(e) of the Consumer Protection Act 1987 states:

> " that the state of scientific and technical knowledge at the relevant time was not such that a producer of products of the same description as the product in question might be expected to have discovered the defect if it had existed in his products while they were under his control."

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[767]DTI (1985) p5.

According to Clark, the European Commission formally protested to the British Government about the change of wording, arguing that this wording would

> " empty the Directive of much of its content."[769]

However, section 1(1) of the Consumer Protection Act states that:

> " This Part shall have effect for the purpose of making such provision as is necessary in order to comply with the product liability Directive and shall be construed accordingly."

Stapleton has suggested that this section and the European Communities Act 1972 will bind any UK court to interpret the wording of the defence in a manner which is consistent with the wording in the Directive.[770] Adding to the controversy, Newdick has suggested that section 4(1)(e) of the Consumer Protection Act has correctly interpreted article 7(e) of the Directive.[771] The Manager of Legal and Administrative Affairs at the ABPI wrote a paper which presented the views of the pharmaceutical industry:

> " The objection which is given the greatest emphasis is that whereby it is stated that the presence of the defence creates a loophole in the legislation in that some injured parties will not succeed in their claims where the defence is pleaded successfully. In this context, the thalidomide tragedy is often referred to and it may be that, in that case, a defence along the lines of the development risks defence could have been successfully invoked. We shall never know. What can be safely said is that, bearing in mind the purpose of the Act, i.e. the protection of the consumer, the defence will be interpreted by the judiciary in favour of the consumer as far as is possible. To allow the defence to be used as a loophole

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[768]Clark (1987) p148.
[769]Ibid..
[770]Stapleton (1994) p52.
[771]Newdick (1988) p475.

would defeat the purposes of the legislation, something the judges would be most careful to guard against." [772]

This report also expresses concern regarding the effect on innovation if the defence were not included:

" It is likely that there would be a change in attitude by pharmaceutical companies from one of being progressive and forward looking to a more defensive, static approach. A reduction in innovation would result in reduced expenditure on research and development and this would have adverse economic consequences, particularly on employment. Companies in other countries without equivalent legislation would be able to be more progressive and could gain an advantage in international markets as a result." [773]

In its analysis of the operation of the Consumer Protection Act, the National Consumer Council discovered that the only case where the development risks defence had been mentioned was the M1 air crash.[774] However, this case was settled out of court and therefore, the defence was not examined. Clark has stated that:

" Unless the defence can be shown to have protected manufacturers against overwhelming liability, as is unlikely to be the case, then the opportunity should be taken to evict from the sphere of strict liability what is effectively a trespasser from the world of negligence. Only then will the policy aims underlying the new regime fully be realised." [775]

In 1996, The European Commission brought an action under Article 169 of the EC Treaty for a declaration that the UK had failed to fulfil its obligations under the Treaty as it had failed properly to implement the Directive 85/374.

" The European Commission contended that the English provision called for subjective assessment in that it placed emphasis on the conduct of the reasonable

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[772]George (1988).
[773]Ibid.
[774]NCC (1995) p23.

> producer, having regard to the standard precautions in use in the industry in question, and therefore broadened the art 7(e) defence, which was based on an objective test (i.e. the state of scientific and technical knowledge, rather than the capacity of producers to discover the defect) and converted the strict liability imposed by art 1 of the directive into liability for negligence."[776]

In 1997, the Court of Justice held that the application by the European Commission would be dismissed for the following reasons:

> (1) On a proper construction of art 7(e) of Directive 85/374, the producer of a defective product had a defence if he could prove that the objective state of scientific and technical knowledge, including the most advanced level of such knowledge, at the time when the product in question was put into circulation was not such as to enable the existence of the defect to be discovered. However, it was implicit in the wording of the directive that that knowledge had to have been accessible at the time when the product in question was put into circulation. On that issue, the directive raised difficulties of interpretation which, in the event of litigation, the national courts would have to resolve having recourse, if necessary to art 177 of the EC Treaty.
>
> (2) On its proper construction, the wording of s.4(1)(e) of the 1987 Act placed the burden of proof on the producer, it placed no restriction on the state of scientific and technical knowledge which was to be taken into account and it did not suggest that the availability of the defence depended on the subjective knowledge of a producer taking reasonable care in the light of standard precautions taken in the industrial sector in question. Further, s.1(1) of the Act expressly provided that the relevant provisions be construed in conformity with the directive and the Commission had provided no evidence to suggest that the English courts would interpret s.4(1)(e) inconsistently

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[775] Clark (1987) p185.
[776] *European Commission v United Kingdom*, (1997) All ER 481.

> with the directive. It followed that the Commission had selectively stressed particular terms used in the English provision without demonstrating that the general legal context of the provision failed effectively to secure full application of the directive."[777]

In relation to this decision, Spink commented:

> " The thalidomide episode became one of the great catalysts for reform of European product liability law in the 1960s. It was the manifest inability of negligence-based systems to compensate adequately and easily victims of the drug that led to the loudest calls for a more effective legislative regime. Regrettably, if one applies the court's interpretation of art 7(e) to that scenario, it is doubtful whether the cause of the thalidomide children would have been significantly furthered by the product liability directive. That is the acid test."[778]

The Author suggests that, although the wording of the development risks defence has been held to be conform to Directive 85/374, the UK could decide to derogate from this defence. This may be just as unlikely as the possibility of an alternative no-fault compensation scheme being introduced; however, until such time as the defence is examined in court in the UK or Europe, its true import cannot be fully examined. As mentioned in Chapter One, a claim against the manufacturers of the oral contraceptives Femodene and Marvelon, (Schering and Organon respectively), is being brought under the Consumer Protection Act 1987. It is alleged that the two companies have been negligent and breached regulations in respect of manufacture, supply, packaging and testing.[779] This may be the long awaited opportunity to test the defence in court and the result could influence the Government's thinking on the defence.

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[777] Ibid pp481-482.
[778] Spink (1997) p418.
[779] Pearson (1997). It is interesting that although this action has been brought under the 1987 Act, the acting solicitors have also alleged that there was negligence on the part of the pharmaceutical companies.

4.14 Conclusions

Although, there has been an increase in the number of actual or potential product liability actions invloving medicinal products, there has not been a case relating to medicinal products which has involved the Consumer Protection Act 1987. This has made it difficult to assess the provisions of the Act.

In assessing whether the legislative framework had achieved a balance between pharmaceutical innovation, consumer safety and legal redress, the Author initially placed as much weight on researching the effect of the product liability scheme on this balance as researching the effect of the regulatory scheme controlling medicinal products on this balance. However, it is now the Author's opinion that the product liability scheme has not played as important a part in the legislative framework regarding the control of medicinal products as the Medicines Act 1968 and the 1994 Regulations.

The only aspect of the product liability scheme which potentially affects the balance of the legislative framework is the development risks defence because of its potential impact on pharmaceutical innovation. The role of warnings is also of importance in any discussion of product liability and has been discussed in detail elsewhere.[780] The Author did not discuss warnings as it was concluded that this was an issue which did not impact on the legislative framework to the same extent as the development risks defence, although it is of greater importance in the regulatory framework.[781]

What must be borne in mind is that the difficulties involved in raising an action in terms of the Consumer Protection Act 1987 do not just extend to an interpretation of

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[780] Clark (1989) p77.
[781] See Section 4.8 "Information to Patients".

the terms of the 1987 Act. There are difficulties which could be encountered in bringing any kind of legal action and these include issues such as legal aid,[782] establishing causation,[783] raising a group action,[784] obtaining access to documents and finding suitable expert witnesses. These difficulties may preclude an action being brought in the first place. These are issues which are discussed in detail elsewhere,[785] although the Author concluded that further research could be conducted into the implications of these procedural issues on legal redress for medicinal products.

Until there are cases involving medicinal products brought under the Consumer Protection Act, the full import of the Act cannot be appreciated fully. The result may make the Government reconsider the position relating to the development risks defence.

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[782] "Legal Aid on trial over drugs", The Herald, 13 February 1997, Sharp (1994), SCOLAG (1997)
[783] Goldberg (1996) and Gordon (1996)
[784] Scottish Law Commission (1993) and (1994).
[785] Goldberg (1996) and Scottish Law Commission (1993) and (1994).

Chapter Five

Summary of Conclusions and Recommendations

5.1 Introduction

On 2 December 1961, thalidomide was withdrawn from the UK market. Worldwide, more than ten thousand children were born with thalidomide-induced injuries. After a protracted campaign in the media, the manufacturers of thalidomide set up a trust fund for these children. However, more than thirty years after its withdrawal, media, public and medical attention is still focused on thalidomide. The reasons for this are that there have been new reports of adverse reactions associated with thalidomide and reports of its use in the treatment of certain diseases, including lepra reaction, rheumatoid arthritis and AIDS-related oral ulcers and cachexia. With regard to the current use of thalidomide, there is great potential risk (for pregnant women) but also immense potential benefit.

It is widely acknowledged that thalidomide instigated law reform in the UK, the European Community and many other countries, in relation to product liability and the regulation of medicinal products. In the UK, a legislative framework relating to medicinal products was introduced following thalidomide. It was argued in this thesis that this framework encompasses a product liability scheme (which applies to all types of products) and a regulatory scheme specifically relating to the control of medicinal products. The recent re-examination of thalidomide in the general media and medical press regarding the controversy surrounding its use, suggested to the Author that the legislative framework introduced following thalidomide should be reviewed in order to discuss current safeguards and analyse whether or not a catastrophe such as that caused by thalidomide could happen again.

It was proposed by the Author that a legislative framework must balance three elements: pharmaceutical innovation, consumer safety and legal redress.

Pharmaceutical innovation refers to the ability of the pharmaceutical industry to develop new products; consumer safety refers to the protection of consumers from the adverse effects of medicinal products; and legal redress refers to the ability of consumers to obtain compensation for injuries caused by medicinal products. The aim of this thesis was to examine the hypothesis that the legislative framework had not struck an appropriate balance between the elements of pharmaceutical innovation, consumer safety and legal redress. For the purposes of this thesis, the "legislative framework" referred not only to the legislation implemented in the UK and Europe following thalidomide, but also regulations relating to medicinal products which have been introduced, including self-regulatory codes, such as, the Code of Practice for the Pharmaceutical Industry.

The examination of this hypothesis was both interesting and important because the legislative framework in the UK, which comprises both national and European legislative provisions, was significantly amended on 1 January 1995 by The Medicines for Human Use (Marketing Authorizations etc.) Regulations 1994. These Regulations introduced a completely new basis for the licensing of medicinal products. Also, the examination of this hypothesis was conducted at a time when there had not been much opportunity for other authors to comment on this new framework.

5.2 The Legislative Framework

By 1978, in relation to the introduction of legislation relating to product liability, there were four major UK and European sets of proposals. These proposals had been issued by the Law Commission and the Scottish Law Commission, the Royal Commission on Civil Liability and Compensation (which concluded that medicinal products should not receive special treatment and should not be exempt from new proposals), the European Commission and the Council of Europe. The proposal from the European Commission was selected to form the basis of the new legislation.

It is widely acknowledged that the development of a Directive from this European proposal was problematic and negotiations continued over a ten year period. It was only by allowing Member States to derogate from the Directive with regard to primary agricultural products, a development risks defence and a financial ceiling on liability that consensus was finally achieved. The "Council Directive of 25 July 1985 on the approximation of laws, regulations and administrative provisions of the Member States concerning liability for defective products" was issued in 1985.

This Directive was implemented into UK legislation by the Consumer Protection Act 1987, which came into force on 1 March 1988. In relation to the derogations allowed in the Directive, the UK has decided not to include primary agricultural products, to include a development risks defence and to exclude a ceiling on financial liability. To date, none of the reported cases which have involved the Directive, as implemented in the Member States, have concerned medicinal products.

In 1995, the European Commission reviewed the operation of the Directive and concluded that the Directive did not require to be amended but that the protection of consumers and the functioning of the Internal Market required continued monitoring.

Legislation relating to the control of medicinal products originated in the mid-nineteenth century and focused initially on the regulation of poisons. Throughout the twentieth century, the development of this legislation was piecemeal and there were many loopholes and anomalies.

There were several missed opportunities for improvements in this legislation including the Report of the Select Committee on Patent Medicines in 1914, an article by Discombe in 1952 and a report by the World Health Organisation in 1957. However, the impetus for reform in the legislation of medicinal products did not occur until 1961, when thalidomide exposed the inadequacies of the existing legislation.

In 1965, the European Commission published the first Directive relating to medicinal products. More Directives relating to medicinal products did not appear until 10 years later. In 1967, the White Paper, "Forthcoming Legislation on the Safety, Quality and Description of Drugs and Medicines" was published in the UK. On 2 February 1968, the Medicines Bill began its passage through Parliament and received the Royal Assent on 25 October 1968. However, it was not until 1 September 1971, the 'first appointed day', that the licensing provisions of the Medicines Act 1968 came into force. Part II of the Medicines Act sets out the main framework of the licensing system with provisions relating to Product Licences, Manufacturer's Licences, Wholesale Dealer's Licences and Clinical Trial Certificates.

The Medicines Act created a series of offences for failure to comply with its provisions. There have been a number of prosecutions for these offences, although it was argued that the fines imposed were too low considering the seriousness of these offences.

The Author found that the discussion of the current legislative framework controlling medicinal products was complicated because of the introduction of a new regulatory scheme by The Medicines for Human Use (Marketing Authorization Etc.)

Regulations 1994 (the "1994 Regulations") on 1 January 1995. The 1994 Regulations implemented a package of European Directives known as the "Future Systems" package, which were designed to complete the EC single market in pharmaceuticals. These Regulations replaced the earlier scheme under the Medicines Act 1968 and consequently replaced this Act as the legal basis for licensing the majority of medicinal products. However, many provisions of the Medicines Act 1968 are still in force and, unfortunately, there has been no consolidation of the legislation. In the opinion of the Author, this has led to there now being an overly complicated regulatory framework which encompasses UK and European legislation, and also self-regulatory codes such as the Code of Practice for the Pharmaceutical Industry.

From 1 January 1995, two new licensing procedures were established : the centralised and decentralised procedures. These procedures replaced the Concertation and multi-state European licensing procedures which, by common consensus, were not a great success.

It was suggested by the Author that the implementation of the "Future Systems" package of legislation was the most important development in the history of the regulation of medicinal products in Europe and the UK since the implementation of the Medicines Act 1968.

The "Health Ministers" and the "Agriculture Ministers" are responsible for the administration of the licensing of medicinal products. This provision is contained in the 1994 Regulations and in the Medicines Act. However, the "day to day responsibilities of medicines control" have been and continue to be delegated by Ministers to the Medicines Control Agency (MCA)

The Author discussed the work of Medicines Division, the Medicines Control Agency, the Medicines Commission, the Committee on Safety of Medicines, the British Pharmacopoeia Commission, the Committee on Dental and Surgical Materials

and the Committee on the Review of Medicines. This provides a comprehensive view of how the Medicines Act 1968 has operated in practice and provides an insight as to the manner most of these bodies will continue to operate under the 1994 Regulations.

The legislative changes contained in the 1994 Regulations have led also to the establishment of the European Agency for the Evaluation of Medicinal Products (EMEA). The EMEA comprises the Committee on Proprietary Medicinal Products (CPMP), the Committee for Veterinary Medicinal Products (CVMP), a Secretariat, and Executive Director and a Management Board.

With the benefit of hindsight, the Author found it surprising that, prior to thalidomide, earlier opportunities for a review of the legislation relating to medicinal products, such as the inter-departmental working party set up in 1959 and the reports by Discombe and the WHO, had been missed. It also seemed surprising that, following thalidomide, it took so long before the Medicines Act 1968 was drafted and then implemented. Also, it took more than 30 years before the provisions of Directive 65/65/EEC were implemented into UK law by the 1994 Regulations. Admittedly, these various UK and European legislative provisions were complicated, but one would have thought that legislation could have been in force more quickly.

Problems relating to the operation of the legislative framework have related to delays associated with applications for clinical trial certificates and bureaucracy associated with the administration of the Medicines Act. However, generally speaking, following the introduction of the Clinical Trial Exemption scheme and the establishment of the Medicines Control Agency, there has not been criticism of the entire legislative framework, more that improvements could be made to certain aspects. Experience with the operation of the 1994 Regulations has been limited but there have not been any reported serious criticisms.

The Author concluded that the main difficulty with the legislative framework is that it is too unwieldy. For example, the Medicines Act 1968 has been amended by over 300 statutory instruments, the 1994 Regulations and many European Directives (which have also been amended). It was suggested that the current legislative framework consisting of the great variety of sources discussed in this Chapter, should be consolidated into a single piece of legislation. Although it was appreciated that this would be a complex drafting exercise, it was thought that this was nevertheless crucial as it would clarify a number of potential ambiguities which have crept into the interpretation of the Medicines Act following the implementation of the 1994 Regulations, particularly in relation to the status of Part II of the Medicines Act. For example, section 19 which sets out provisions relating to safety, quality and efficacy in the regulation of medicinal products is still in force but has not been amended by the 1994 Regulations to refer to marketing authorisations instead of product licences. Statutory instruments will continue to amend the new legislative framework, but it was suggested by the Author that each new statutory instrument should consolidate earlier statutory instruments.

5.3 Methodology

The aim of this thesis was to analyse the effect of the legislative framework on consumer safety, pharmaceutical innovation and legal redress. To this end, the Author had to gather a diverse range of materials relating to medicinal products which included legislation, regulations, guidelines, leaflets, books and articles from a variety of medical, scientific and legal sources. The investigation of these sources involved a full analysis of material at the interface of medicine, science and law. Although the analysis of these sources was conducted from the Author's legal perspective, the Author placed as much emphasis on the medical and scientific sources as the legal sources.

It was suggested that this approach of treating these medical, scientific and legal sources as being of equal importance and as interacting with one another, was the only means by which this thesis could have been properly researched. If these sources had been looked at in isolation or from the perspective of being of unequal importance then the Author would not have been fully aware of the extent of the legislative framework and the manner in which it operated in practice.

In the course of researching this thesis, the Author has concentrated on examining published sources rather than conducting empirical research and focused on an analysis of the legislative framework in the UK rather than conducting a comparative study with other jurisdictions, because there was plenty of new UK and EC material to analyse.

The Author contacted experts from the pharmaceutical industry, the Medicines Control Agency, the CSM, the CRM, the ABPI, the Royal Pharmaceutical Society of Great Britain, several research organisations and consumer organisations. The

discussions with these experts verified the research emphasis of this thesis and confirmed the focus which the thesis would take.

The Author used sources such as: articles in the lay press; television programmes; cross-references from books and articles; and the pharmaceutical and medical library collections in the University of Strathclyde, University of Glasgow (which is also a depository for materials published by the European Commission) and the Drug Information Centre in the Royal Infirmary, Glasgow. These sources provided a great deal of useful background information. However, to achieve a greater depth of information, the Author constructed a "formal" research strategy, which involved a systematic check of sources. This strategy was in four stages:

1. Primary legal sources including legislation;

2. Organisations which were involved in the legislative framework;

3. Bibliographic searches; and

4. The Internet

This thesis considered the effect of primary UK legislation (Medicines Act 1968, and the Consumer Protection Act 1987) and secondary UK legislation (over 300 statutory instruments) in relation to the regulation of medicinal products. The Author concluded that European legislation had become increasingly important because of the introduction of the centralised and decentralised licensing procedures in the UK, which implemented Directive 65/65/EEC. Up until this point, European legislation had seemed more like a completely separate legislative framework. The introduction of this new legislative framework integrated UK and European legislation. However, this was not a European law thesis and the analysis of European law in this thesis was purely from a UK perspective.

The Author consulted every relevant European directive, regulation, decision, recommendation, opinion and guideline which related to medicinal products or medical devices for human use, issued between 1965 and 1997. Directives are the most often used type of legislation for the introduction of new European legislative provisions relating to medicinal products. Directives are binding on Member States with regard to their objectives but allow the Member States to implement the provisions of the Directives into their national law by the most suitable means. In the UK, directives are implemented by way of statutory instruments.

Information from the following organisations was examined: the MCA, the EMEA, the Medicines Commission, the CSM and the other Section 4 Committees, the CSD, the MDA, the Royal Pharmaceutical Society of Great Britain, the CMR, the Center for the Study of Drug Development, Social Audit, the British Institute for Regulatory Affairs, the Proprietary Association of Great Britain, the Drug Safety Research Unit, the National Consumer Council, Action for Victims of Medical Accidents, the General Medical Council, the Office of Health Economics, the Medical Benefit/Risk Foundation; the Institute of Economic Affairs; the Legal Aid Board; and the Law Society of Scotland.

The Author gathered additional material by obtaining references from various medical, scientific and legal bibliographic indexes and used the Internet as a means of keeping up-to-date with recent developments relating to the regulation of medicinal products. The websites consulted included organisations such as: the ABPI; The British Medical Journal; the British Institute of Regulatory Affairs; the CSM; Europa; the EMEA; HMSO; The Lancet; the MDA; the MCA; the Department of Health; Houses of Parliament; the US FDA; and the World Health Organisation.

The Author concluded that as much information as possible should be made available on the Internet and that the MCA and CSM should follow the example of the

EMEA, which had a excellent website. Not only did the EMEA make its publications available on the Internet, but it also issued press releases giving a detailed account of the activities of the CPMP and the Management Board.

It was also concluded that the most useful tool for examining primary as well as secondary materials at the interface of medicine, science and the law was the Internet. Although use of the Internet did not completely replace the need to use more traditional bibliographic search indexes in the initial stages of research, it did replace the need to keep visiting the library for the purposes of keeping up-to-date with new developments and the need to contact organisations in order to obtain copies of new material, as most organisations make new material available on the Internet. The Author found that new information and websites relevant to medicinal products appear on a regular basis.

A copy of the Food, Drug and Cosmetic Act is available on the FDA's website and it was suggested that access to an overview of the legislative framework operating in the UK on the MCA's website would be extremely helpful. Unfortunately, the legislative provisions relating to medicinal products are scattered throughout UK and European legislation, which has been constantly amended (and not to any great extent consolidated), and it may be too ambitious to hope that this information could be available on the Internet. Transparency relating to the activities of the regulatory agencies is to be encouraged and this could be achieved by development of the information available on the Internet.

5.4 Pharmaceutical Innovation

Pharmaceutical innovation is the most important area of effort for research-based pharmaceutical companies and expenditure on pharmaceutical research and development amounts to more than £2 billion per year. It takes 10 to 12 years to develop a new medicinal product and this process costs more than £200m. It is widely regarded that the introduction of new medicinal products is beneficial not only to patients but also to the economy. Therefore, it is important that pharmaceutical innovation leading to the introduction of new medicinal products is not hindered by the legislative framework.

As far as pharmaceutical innovation is concerned, it was suggested that, from an industry perspective, issues such as patent protection and the decline in the university science base are believed to have a greater impact on innovation than the regulatory requirements imposed by the legislative framework.

No reports were found in the medical, scientific or legal materials which claimed that specific medicinal products had not been introduced because of excessive regulation or threat of legal action in the UK; this contrasts with the USA, where litigation has allegedly delayed the introduction of products such as oral contraceptives and vaccines. Certainly in the past, aspects of licensing, specifically applications for clinical trial certificates, delays at Medicines Division and delays in the multi-state and concertation licensing procedures were of concern to the pharmaceutical industry in relation to innovation. The Author could not find evidence of recent industry complaints relating to the legislative framework.

However, what would be of concern is if the centralised and decentralised licensing procedures introduced by the 1994 Regulations degenerate into bureaucratic and

complicated licensing systems. It was suggested that a measure of the bureaucracy of a licensing procedure is the length of time it takes for a medicinal product to be licensed. In relation to centralised applications, there have been no reports of there having been delays in the times taken to process these types of applications, despite there having been an increase in the number of applications in 1996. In addition, in a limited number of applications for medicinal products used in the treatment of serious disease, the EMEA has been able to accelerate the time taken to evaluate these types of products

In relation to the decentralised procedure, there have been more serious delays reported with regard to the processing of applications. However, following the initial problems reported by the EMEA, the use of this procedure has increased. A difficulty with the decentralised procedure would be if there were variations in standards between the Competent Authorities of the Member States. However, no evidence was found of this problem developing. The UK is the leading reference state and one of the major rapporteurs or co-rapporteurs for these licensing procedures, and there has been no reported criticism of the MCA as having dropped its evaluation standards to inflate its approval rates in order to attract more applications.

The main difficulty in assessing the operation of the centralised and decentralised procedures, is that there has just not been enough experience with these new procedures to conclude how effectively they are operating. However, it would appear, that regulatory officials and the pharmaceutical industry are working together to achieve an efficient regulatory system. Also, there have been no reports in the medical press of complaints from the industry relating to delays in licensing.

On the basis of the evidence available, it was suggested that the operation of these new licensing procedures has not been so overly bureaucratic as to have had a negative impact on pharmaceutical innovation.

5.5 Consumer Safety

The media has had an increasingly influential role with regard to influencing public opinion on issues concerning medicinal products, particularly consumer safety. Many writers have commented on the worrying concept of "trial by television", particularly, as in recent years, there has been an apparent increase in "exposé" programmes relating to medicinal products. The difficulty experienced by the Author was in determining the true extent of any threat to consumer safety posed by the ineffective control of medicinal products by the legislative framework.

In the years following thalidomide, there were a number of well-publicised withdrawals of medicinal products and medical devices, and reports of serious adverse reactions. The CSM receives reports of suspected adverse reactions to medicinal products and it is accepted that adverse reactions are under-reported. It is unclear what percentage of hospital admissions are caused by adverse reactions to medicinal products: estimates vary from 2,500 deaths to 240,000 hospitalisations. There may be disagreement over the actual incidence of adverse reactions, but it is clear that there are risks, as well as benefits, involved in taking medicinal products.

The assumption is that threats to consumer safety originate from inherent or design defects in medicinal products. However, it was suggested by the Author that there are potential risks to consumer safety from fraud and misconduct in medical research, counterfeit medicinal products, defective medicinal products, herbal products, homeopathic products, excipients in medicinal products, health frauds, deliberate or accidental overdoses, any breach of the regulations relating to control of medicinal products, prescribing errors by doctors and dispensing errors by pharmacists. It was suggested that these risks to consumer safety should be further researched and that the

risks quantified. Many of these potential risks are not controlled by the legislative framework.

The Author examined a selection of medicinal products and medical devices which have raised general concern as to how well consumers have been protected from injury: benoxaprofen (Opren), benzodiazepines, iophendylate (Myodil), heart valves, practolol (Eraldin), paracetamol and aspirin. The Author used these medicinal products to determine specific criticisms of the regulatory system and these criticisms included: the monitoring of adverse reactions; information supplied to patients; the promotion of medicinal products; conflicts of interest within the regulatory process; the scope of products regulated by the legislative framework; and the legal status of medicinal products.

The Author considered that a possible safety concern for consumers was from products which have been reported to cause adverse reactions, but were not controlled by the legislative framework. "Relevant medicinal products" are regulated by the 1994 Regulations. It was of concern to the Author that products such as medical devices, products supplied on a "named patient" basis, homeopathic products and herbal products are not controlled by these Regulations; particularly since these products have been associated with serious adverse reactions.

The regulation of homeopathic medicinal products has become increasingly important because it has been reported recently that the homeopathic market will grow considerably in the UK over the next 5 to 10 years. Although these products do not generally present a safety risk, a registration scheme is now in operation and this was considered by the Author to be a definite improvement. However, the Advisory Board overseeing homeopathic products does not seem to be receiving sufficient work and there have not been many applications for registration under the scheme. It was

suggested that the remit of the Advisory Board should be extended to include herbal products and that the operation of this scheme should be monitored.

There have been many serious adverse reactions and some deaths associated with the use of herbal products, and there is considerable body of evidence to support the assertion that "natural does not mean safe"; even certain herbal teas have serious side effects. Some herbal products are covered by the legislative framework, however, it was concluded that the position of the exempted herbal products needed to be re-examined. Indeed, pilot studies have been set up in a number of European countries to monitor the safety of herbal products. The CSM has extended the Yellow Card scheme to include adverse reactions to unlicensed herbal medicines. It is the opinion of the Author that these products should be brought under the control of the legislative framework.

It was concluded that it is unclear exactly how many unlicensed medicinal products are prescribed on a named patient basis. This fact alone is of concern. Thalidomide with its well documented risk of adverse reactions is an example of an unlicensed medicinal product. It is clear that there are a number of circumstances in which doctors are justified in prescribing on a named patient basis This practice is clearly set to continue and unless these products are brought within the control of the legislative framework, the alternative is that patients and prescribers fall outwith the "protection" of the legislation.

Certain medical devices have caused serious adverse reactions and deaths, and the regulation of medical devices has always been a controversial issue. Some of these devices were controlled by the Medicines Act 1968; now all are controlled by a combination of European Directives administered by the Medical Devices Agency (MDA). There have been several high profile claims for compensation involving adverse reactions which have occurred with medical devices, such as Bjork Shiley

heart valves, silicone breast implants and the Dalkon Shield intrauterine contraceptive device. The new regulations relating to medical devices are a definite improvement and although there has not been much experience with these regulations, the Author concluded that the MDA was operating very efficiently, but, as with the homeopathic registration scheme, it remained to be seen how effective the regulatory scheme will be over the coming years.

It was suggested that the independence and impartiality of committees is of crucial importance. In order to avoid potential conflicts of interest within the legislative framework, Regulation 2309/93 specifies that the membership of Committees such as the CPMP will be made public, the professional qualifications of each member given and that there should not be any financial or other interests in the pharmaceutical industry which could affect impartiality. In the UK, "Declaration of Interests: A Code of Conduct for Members of the Medicines Commission and Section 4 Committees and Sub-Committees", operates to control the disclosure of interests in the pharmaceutical industry.

There have been allegations that there are conflicts of interest within the Medicines Commission and the CSM. The Author analysed the declared interests of the Medicines Commission and the CSM, and concluded that there was no evidence of there being any conflict of interest. It was concluded that it was inevitable that well-respected academics who are Committee members will be offered consultancies by the pharmaceutical industry. It was argued by the Author that participation in the commercial research and development of medicinal products is not necessarily detrimental to the process of licensing medicinal products as the Committee members with commercial interests will have insight into current industry practices. It was further argued that the existence of these interests does not mean that the CSM is not able to make impartial decisions. However, conflicts of interest must be monitored in order to prevent any problem emerging.

It is possible for the legal status of a medicinal product to be changed by statutory instrument. It was suggested that consumers should be given as much choice as possible, however, safety was paramount. Increasing numbers of products have been "switched" from prescription only to pharmacy status, and from pharmacy to general sale list status. Despite stringent controls, terfenadine has had to be returned to prescription control because of the threat of serious adverse reactions and certain medicinal products available on general sale are now under stricter control. If "riskier" medicinal products are to be made more freely available to consumers then the Author argued that not only should there be stronger sanctions against pharmacists who do not supervise the sale of medicinal products as this supervision protects consumers, but there should be better information for consumers about medicinal products, so as they can make informed decisions about the medicinal products they purchase. In addition, community pharmacists should be allowed to monitor the safety of the medicinal products they dispense and report any adverse reactions via the Yellow Card Scheme.

Information relating to medicinal products is available from doctors, pharmacists, patient information leaflets, other consumers and the media. Unfortunately, the development of the concept of "trial by television" has meant that patients are not necessarily being given accurate and impartial information about medicinal products. The most detailed advice which a patient will receive about a medicinal product will originate from a patient information leaflet. It was the opinion of the Author that the benefits of giving patients information about the medicinal products they ingest, outweighs any disadvantages such as, concern that a patient may be too frightened to take a medicinal product or that the doctor/patient relationship may be harmed in some way.

From the perspective of consumer safety, the information given in patient information leaflets about specific medicinal products is more important to the consumer, as these leaflets warn of adverse reactions and contra-indications, than any

information given about the operation of the legislative framework and the process by which medicinal products are regulated. However, the Author suggested that transparency about the operation of the legislative framework should be encouraged as it would make consumers more conscious of the means by which medicinal products are regulated and the organisations who are involved in regulating these products. There have, however, been problems in implementing this transparency, although the EMEA has been successful in publishing information on the Internet.

The promotion of medicinal products by the pharmaceutical industry has been criticised by the media on a number of occasions and the ethical implications of the relationship between the pharmaceutical industry and medical profession has been the subject of much discussion in the medical press. Regulations were introduced in 1994 which created offences related to various promotional activities. However, there have been no prosecutions under these regulations and the Government recently introduced a "clampdown" on pharmaceutical companies and wholesalers who offer gifts and inducements, which will entail these regulations being strengthened. This is to be encouraged as it is in the interests of consumer safety for medicinal products to be supplied on the basis of benefit to the patient as opposed to occurring on the basis of advertising or any other promotional practice. Statutory penalties should be utilised to curb undesirable promotional activities.

The promotional activities of the pharmaceutical industry are also controlled by self-regulation by the PMCPA, which operates in terms of the "Code of Practice for the Pharmaceutical Industry". It has been stated that promotional activities are kept "generally well in check" by this self-regulation. However, it was observed by the Author that there had been a steady rise in the numbers of cases which have been reported as having allegedly breached the Code of Practice. It was unclear whether this increase is due to a perceived decline in the standard of promotional practices used by the pharmaceutical industry or whether there has been an improvement in the

reporting these alleged breaches. Certainly, the PMCPA have adopted a more "transparent" attitude to their investigation of alleged breaches and this may have encouraged health professionals and others to report suspected breaches.

The Author analysed breaches of the Code of Practice and collated information relating to the medicinal products involved, the complainants involved, the companies which have breached the Code and the sections of the Code which were breached. It was found that most complaints came from health professionals and, in particular, general practitioners.

The Author suggested that the most serious breach of the Code of Practice was a breach of Clause 2, "Methods of Promotion". This clause has been breached a total of 50 times. The most breached clause of the Code of Practice is Clause 7 "Information, Claims and Comparisons", which has been breached 640 times. Clause 7.2 which refers to information, claims and comparisons being accurate, balanced, fair, objective, unambiguous and based on an up-to-date evaluation of evidence has been particularly breached.

The Author concluded that although the PMCPA investigated the breaches of the Code effectively and efficiently, it did not have access to sufficiently severe sanctions to deal with more serious breaches of the Code of Practice. Therefore, the Author suggested that use should be made of the more severe sanctions contained in the Regulations and that companies should be fined for conducting unacceptable promotional activities. It remains to be seen whether or not the Licensing Authority will prosecute offences which are in breach of the Advertising Regulations, or if the cases will continue to be referred to the PMCPA.

It is widely acknowledged that adverse reactions to medicinal products are under-reported. Adverse reactions to medicinal products are reported to the CSM on a voluntary basis by doctors, dentists, hospital pharmacists and HM Coroners under the

"Yellow Card scheme". Reports are also received from pharmaceutical companies as a condition of their licences. The CSM has undertaken various measures to encourage the reporting of adverse reactions and recently all hospital pharmacists were given permission to make yellow card reports. A pilot scheme for community pharmacists is now operating and it is the opinion of the Author that all community pharmacists should be allowed to make yellow card reports, as this could possibly reverse the trend of the under-reporting of adverse reactions, particularly as there are many former prescription only products which are now available over-the-counter from pharmacies. As a further means of encouraging the reporting of adverse reactions, it was suggested that, in the future, the possibility of limited reporting by patients should be considered.

Once an adverse reaction has been identified, the following may occur:

- there may be no action as it is a well-recognised adverse reaction and the risks of continuing to use the medicinal product do not outweigh the benefits;
- there may be a report in the medical literature or Current Problems in Pharmacovigilance and medicinal product may be asked to be more closely monitored by health professionals;
- there may be a variation to the product licence/marketing authorisation (warning strengthened in product literature, use controlled etc.);
- the Health Ministers may issue a Section 62 Order which prohibits the sale, supply or importation of the specified medicinal product, where deemed necessary to do so in the interests of safety;
- the medicinal product may be withdrawn voluntarily from the market; or
- the product licence/marketing authorisation may be revoked.

The Author suggested that, where possible, licences should not be withdrawn as there will always be some patients who have responded well to that particular medicinal product. For example, it has been recently found that thalidomide has great benefits to patients with HIV. Thalidomide is used on a named patient basis and the Author suggested that, if it were licensed, then greater control could be exercised over its use, just as is done with the teratogenic medicinal product, RoAccutane. Therefore, it would be possible to license even the most potentially "dangerous" medicinal products and use them with an acceptable risk/benefit ratio by communicating the risks to health professionals and patients, in CSM publications and in product literature.

It was concluded that there should be transparency relating to the way in which decisions on adverse reactions are made, and as much information as possible should be communicated to patients about adverse reactions to medicinal products. In 1995, the way in which information regarding the safety of certain types of oral contraceptives was conveyed to health professionals and the public was heavily criticised. This led to a "pill scare" among patients and a rise in abortions was reported by the British Pregnancy Advisory Service.

5.6 Legal Redress

There has been an increase in the number of actual or potential product liability actions involving medicinal products. However, very few of these actions have been resolved by court action, most have been decided by out-of-court settlements and there have been no reported cases involving the Consumer Protection Act 1987. This increase suggested to the Author that this may be an illustration of a failing in the legislative framework from the perspective that consumers were experiencing safety problems with certain medicinal products. Also, the fact that that there has been no action taken under the Consumer Protection Act 1987 suggested to the Author that there could be a problem with the system by which consumers sought legal redress.

Most discussions involving issues of legal redress regarding medical negligence or product liability relating to medicinal products inevitably centre on proposals for a no-fault compensation scheme such as is operated in New Zealand or an insurance scheme such as is operated in countries such as Sweden, Finland and Japan. Such discussions, although of general interest, are not of relevance to the development of an alternative scheme of compensation in respect of product liability in Europe. It is argued by the Author that the current system of product liability will not be set aside in favour of an alternative scheme owing to the extensive discussions, conducted at UK and European level which excluded the proposal that medicinal products should be treated separately from other products, and which eventually culminated in the 1985 Directive and the enactment of the Consumer Protection Act 1987.

However, two alternative compensation schemes relating to medicinal products operate in the UK: the vaccine damage payments scheme and the clinical trial compensation scheme. This demonstrates that there is a precedent for treating

medicinal products differently from other types of product. However, it was suggested by the Author that neither of these schemes could form the basis of a viable replacement scheme for medicinal products in place of the Consumer Protection Act 1987.

Another alternative is that the Government has instituted its own compensation scheme in relation to HIV-contaminated blood and blood products and contaminated human growth hormone. It was suggested by the Author that these Government schemes were instituted because these products were not subject to any control under the Medicines Act 1968 and the Government were under pressure to provide compensation. This type of compensation scheme is also not a viable replacement for the Consumer Protection Act.

The problem is that it is difficult to assess how "successful" the Consumer Protection Act 1987 will be in relation to providing legal redress relating to medicinal products as, although the Act has been in effect since 1 March 1988, there have been no reported cases under the Act involving medicinal products. Despite the lack of reported cases, it is clear that the most controversial aspect of the Consumer Protection Act 1987, in relation to medicinal products, is the development risks defence with its potential impact on pharmaceutical innovation.

The Author suggests that, although the wording of the development risks defence has been held to be conform to Directive 85/374, the UK could decide to derogate from this defence. This may be just as unlikely as the possibility of an alternative no-fault compensation scheme being introduced; however, until such time as the defence is examined in court in the UK or Europe, its true import cannot be fully examined.

What must be borne in mind is that the difficulties involved in raising an action in terms of the Consumer Protection Act 1987 do not just extend to an interpretation of the terms of the 1987 Act. Issues such as legal aid, establishing causation, raising a

group action, obtaining access to documents and finding suitable expert witnesses may preclude an action being brought in the first place. It is the opinion of the Author that further research requires to be conducted into the implications of these procedural issues on legal redress for medicinal products.

In assessing whether the legislative framework had achieved a balance between pharmaceutical innovation, consumer safety and legal redress, the Author placed as much weight on researching the effect of the product liability scheme on this balance as researching the effect of the regulatory scheme controlling medicinal products on this balance. However, it is now the Author's opinion that the product liability scheme has not played as important a part in the legislative framework regarding the control of medicinal products as the Medicines Act 1968 and the 1994 Regulations.

5.7 Final Conclusions

This thesis has examined the hypothesis that the legislative framework had not achieved an appropriate balance between pharmaceutical innovation, consumer safety and legal redress.

It is the opinion of the Author, that, at the present time, a balance has been achieved between these three elements, albeit an imperfect balance, as there could be various improvements made in relation to, for example, promotion, pharmacovigilance and patient information.

There is no evidence to suggest that the interaction of any of these three elements negatively affects the others; although, in the past, bureaucracy in the licensing system may have had an adverse effect on pharmaceutical innovation. However, experience with the 1994 Regulations and the Consumer Protection Act 1987 is limited.

There is no evidence to suggest that the regulation of any of these elements positively affects the others. However, once again, experience with the 1994 Regulations and the Consumer Protection Act 1987 is limited.

However, this balance must be continuously monitored, and it is suggested by the Author that issues such as patents, prescribing errors and legal aid, which are outside the control of the Medicines Act, the 1994 Regulations and the Consumer Protection Act, have greater potential impact on pharmaceutical innovation, consumer safety and legal redress.

5.8 Future Research

The Author has examined many aspects of the regulatory system relating to medicinal products. However, the following areas are suggested as being issues for future research:

- The operation of the Marketing Authorizations Etc. Regulations 1994, including issues such as prosecutions;

- The operation of the centralised and decentralised licensing procedures with specific reference to issues such as "drug lag";

- The development of the roles of the EMEA, CPMP, MCA and CSM;

- The regulation of medical devices and the work of the MDA;

- The regulation of homeopathic and herbal products;

- Transparency of the regulatory system, with reference to the use of the Internet and the proposed Freedom of Information Act;

- The improvement of information supplied to patients;

- The encouragement of adverse reaction reporting, including, for example, the development of scheme involving patients;

- The future of legal aid and group actions involving medicinal product;

- The development of alternatives to clinical trials using animals and humans;

- The improvement of prescribing and dispensing practices;

- An analysis of the level of hospitalisations due to adverse reactions to medicinal products;
- The control of the promotional activities of the pharmaceutical industry;
- The development of systems for the detection of counterfeit medicinal products;
- The regulation of generic medicinal products;
- The pricing structure relative to medicinal products;
- Patents and trademarks relating to medicinal products; and
- The effect of the legislative framework on the introduction of treatments for AIDS.

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G. JOURNAL ABBREVIATIONS

ADR Bull	Adverse Drug Reaction Bulletin
Adv Drug React Ac Pois Rev	Adverse Drug Reactions and Acute Poisoning Review
Adverse Drug React Toxicol Rev	Adverse Drug Reactions and Toxicological Reviews
AJDC	American Journal of Diseases in Children
AJPH	American Journal of Public Health
Am J Comp Law	American Journal of Comparative Law
Am J Hosp Pharm	American Journal of Hospital Pharmacy
Am J Law Med	American Journal of Law and Medicine
Am J Nursing	American Journal of Nursing
Am J Obstet Gynecol	American Journal of Obstetrics and Gynecology
Am J Psychiatry	American Journal of Psychiatry
Am J Public Health	American Journal of Public Health
Am Pharm	American Pharmacy
Ann Intern Med	Annals of Internal Medicine
Ann Thorac Surg	Annals of Thoracic Surgery
Arch Neurol	Archives of Neurology
Arch Toxicol	Archives of Toxicology
BMJ	British Medical Journal
Br J Clin Pharmacol	British Journal of Clinical Pharmacology
Brit J Psych	British Journal of Psychiatry
Can Med Assoc J	Canadian Medical Association Journal
CLB	Commonwealth Law Bulletin
Clin Pharmacol Ther	Clinical Pharmacology and Therapeutics
Clin Res Practices & Drug Reg Affairs	Clinical Research Practices and Drug Regulatory Affairs
DICP	Drug Intelligence and Clinical Pharmacy
DN&P	Drug News and Perspectives
Drug Dev Ind Pharm	Drug Development and Industrial Pharmacy
Drug Inf J	Drug Information Journal
Drug Ther Bull	Drug and Therapeutics Bulletin
Eur J Clin Pharmacol	European Journal of Clinical Pharmacology
FDCLJ	Food Drug Cosmetic Law Journal
Hosp Formul	Hospital Formulary
Int Pharm J	International Pharmacy Journal
J Chron Dis	Journal of Chronic Diseases
J Clin Pharm	Journal of Clinical Pharmacy
J Clin Pharm Ther	Journal of Clinical Pharmacy and Therapeutics
J Clin Pharmacol	Journal of Clinical Pharmacology

J Clin Psychopharmacol	Journal of Clinical Psychopharmacology
J Clin Res Drug Dev	Journal of Clinical Research and Drug Development
J Clin Res Pharmacoepidemiol	Journal of Clinical Research and Pharmacoepidemiology
J Ethnopharmacol	Journal of Ethnopharmacology
J Intern Med	Journal of Internal Medicine
J Law Soc	Journal of Law and Society
J Med Ethics	Journal of Medical Ethics
J Nat Cancer Inst	Journal of the National Cancer Institute
J Parenter Sci Technol	Journal of Parenteral Science and Technology
J Pharm Pharmacol	Journal of Pharmacy and Pharmacology
J Pharm Tech	Journal of Pharmaceutical Technology
J Royal Coll GPs	Journal of the Royal College of General Practitioners
J Royal Soc Medicine	Journal of the Royal Society of Medicine
J Soc Admin Pharm	Journal of Social and Administrative Pharmacy
JAMA	Journal of the American Medical Association
Law Soc Gaz	Law Society's Gazette
Med J Aust	Medical Journal of Australia
Med Toxicol	Medical Toxicology
MIMS	Monthly Index of Medical Specialities
MLR	Modern Law Review
N Engl J Med	New England Journal of Medicine
Perspect Biol Med	Perspectives in Biology and Medicine
Pharm Ind	Pharmaceutische Industrie
Pharm J	Pharmaceutical Journal
Pharm Med	Pharmaceutical Medicine
Prod Liab Int	Product Liability International
Regul Toxicol Pharmacol	Regulatory Toxicology and Pharmacology
Soc Sci Med	Social Science and Medicine
Sol J	Solicitors' Journal
Tort Ins L J	Tort and Insurance Law Journal

H. ORGANISATION ABBREVIATIONS

ABPI	Association of the British Pharmaceutical Industry
BMA	British Medical Association
CMR	Centre for Medicines Research
CSD	Committee on Safety of Drugs
CSDD	Center for the Study of Drug Development
CSM	Committee on Safety of Medicines
MCA	Medicines Control Agency
Med Div	Medicines Division

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