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

Volume Two

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PhD

1998

Appendices

Appendix I

The Discovery and Development of a New Medicinal Product

(Source: Booklet published by Wellcome Research Laboratories in 1988)

I. RESEARCH CONCEPT AND DISCOVERY OF ACTIVE LEAD COMPOUND	II. PRECLINICAL TESTING
approx. 2-20 years research	approx. 2-3 years development
approx. 8000-10000 potential candidate substances	approx. 20-30 remaining substances / approx. 5-10 remaining substances

Research Target	Discovery of Lead Compound	Selection of Product Candidate	Biological Tests	Regulatory Clearance
Therapeutic target Potential commercial target Creation of laboratory target Literature search Research planning Selection of chemical/ pharmacological approach	Extraction/ synthesis of active substances at laboratory scale Creation of pharmacological/ animal model Evaluation of potentially active compounds Selection of potential leads	Patent evaluation Patent application Basic pharmacological and biochemical screening Analytical characterisation of active substances	Acute toxicity - single administration to 2 animal species Detailed pharmacological and biochemical studies (main effects, side effects, duration of effects) Pharmacokinetics - absorption - distribution - metabolism - excretion Subacute toxicity - repeat administration (medium term) to 2 animal species Reproduction and toxicological studies - fertility - teratogenicity - peri and post natal toxicity Mutagenicity tests	Preparation of dossiers/ summary documents of all relevant data for application to licensing authority for clinical trials Presentation of data to ethical committees prior to clinical evaluation

Pharmacy/ Chemical Development
Development of specific analytical methods for active substances, their degradation products and possible impurities
Preformulation studies to determine formulation constraints and possibilities
Synthesis of active substance at technical scale
Consideration of alternative routes of synthesis of active substance
Preparation of model formulations for clinical and toxicological evaluation
Synthesis of radiolabelled compound for pharmacokinetic studies
Development of analytical methodology (stability indicating) for model dosage forms
Stability testing of active substances and model formulations
Production of formulation of active substance and comparison formulations for clinical trials

III. CLINICAL TRIALS	IV. REGISTRATION, LAUNCH AND SALES
approx. 3-5 years development	approx. 2-3 years development
approx. 4-5 remaining substances; approx. 2-3 remaining substances; 1 remaining substance	1 remaining substance

Clinical Trials Phase I	Clinical Trials Phase II	Clinical Trials Phase III	Registration with Health Authorities	Launch and Sales
Tolerability in healthy volunteers - highest tolerable dose - smallest effective dose - dose/effect relationship - duration of effect - side effects Pharmacokinetics in man	First controlled trials on efficacy in the patient Bioavailability testing of formulations	Therapeutic large-scale trials at several trial centres and different patient populations for final establishment of the therapeutic profile - indications - dosage and types of administration - contra-indications - side-effects - precautionary measures Proof of efficacy and safety in long-term administration Demonstration of therapeutic advantage Certification of any iteration with concomitant medication	Documentation of all relevant data for application for registration - expert opinion on clinical trials - expert opinion on pharmacological data - expert opinion on toxicological trials - expert opinion on analytical pharmaceutical trials	Scheduling, ordering and production of the final dosage form, packaging and product literature Quality control for release of products Distribution of products Organisation of symposia

Biological Tests	
Subchronic toxicity (other animal species)	Chronic toxicity - repeat administration (long term) Carcinogenicity studies Supplementary animal pharmacology

Preparation for Launch
Marketing Plan (positioning)
Training of sales force
Information for doctors, wholesalers and pharmacists
Design and preparation of packaging materials
Construction/commissioning of chemical plant at full scale
Validation of manufacturing processes
Development of quality assurance, in-process control procedures
Construction and commissioning of secondary pharmaceutical manufacturing unit

Pharmacy/Chemical Development	
Scale-up of chemical synthesis to pilot plant Development of analytical methods for Q.C. testing Development of variety of formulations e.g.. tablets, injection, topical In-vitro availability tests of formulation Process patent evaluation and application Development of process for manufacture of formulation	Design of chemical manufacturing plant Design of process for secondary pharmaceutical manufacture Confirmation of stability of products in the final packs Validation and finalisation of Q.C. methodology and specifications

Appendix II

Medicinal Products, Medical Devices and Miscellaneous "Medical" Products listed in the "Report Worldwide" column (1990 - 1997)

Medicinal Products, Medical Devices and Miscellaneous "Medical" Products listed in the "Report Worldwide" column published in Product Liability International and in "Liability, Risks & Insurance" (1990 - 1997).[786]

The entries in bold type indicate reports from the United Kingdom.

ACE inhibitors. [Potential legal action ?; USA; March 1992]
Albuminar. [Potential legal action?; USA; October 1996]
Albuterol. [Legal action; USA; February 1994, December 1994 and September 1995]
Alpha Interferon. [Potential legal action ?; Japan; April 1994]
Androcur. [Potential legal action ?; Germany; September 1994, October 1994 and December 1994]
Antibiotics (Generic ingredients). [Potential legal action ?; USA; November 1996]
Aspirin. [Legal action; USA; January 1994]
AZT. [Legal action; UK; January 1994]
Baby oil. [Legal action; USA; October 1990 and December 1991]
Bendectin (known as Debendox in the UK). [Legal action; USA; March 1990 and October 1991]
Benzodiazepines. [Legal action; UK; April 1991, July 1991, April 1994 and April 1997]
Blood given by donor with Creutzfeldt-Jakob disease. [Potential legal action ?; Canada; August 1995]
Blood products contaminated with hepatitis C. [Legal action; UK and Ireland; December 1994, February 1995 and May 1995]
Blood products contaminated with hepatitis B. [Potential legal action ?; UK; May 1990]
Blood products contaminated with hepatitis G. [Potential legal action ?; UK; February 1996]

[786]See entry in the bibliography under "Product Liability International" and "Liability, Risks and Insurance.

Blood products contaminated with HIV. [Legal action and potential legal action ?; UK, Australia, Canada, Denmark, France, Greece, Germany, Ireland, Japan, Malaysia and Sweden; January 1990, May 1990, August 1990, September 1990, December 1990, May 1991, June 1991, November 1991, December 1991, January 1992, March 1992, June 1992, July 1992; August 1992, November 1992, December 1992, January 1993, April 1993, May 1993, June 1993, July 1993, August 1993, October 1993, November 1993, December 1993, February 1994, April 1994, May 1994, June 1994, September 1994, December 1994 , April 1995, September 1995, March 1996, May 1996, June 1996, September 1996, October 1996, November 1996 and April 1997]

Blood storage bags. [Potential legal action?; UK; July 1995]

Breast implants (polyurethane). [Potential legal action ?; USA; November 1993]

Breast implants (saline). [Potential legal action ?; USA; December 1992]

Breast Implants (silicone). [Legal action and potential legal action ?; USA, UK, Canada and Japan; November 1991, January 1992, February 1992, March 1992, May 1992, July 1992, January 1993, March 1993, May 1993, July 1993, September 1993, October 1993, March 1994, April 1994, May 1994, August 1994, September 1994, October 1994, December 1994, January 1995, March 1995, April 1995, May 1995, July 1995, September 1995, October 1995, November 1995, December 1995, January 1996, March 1996, May 1996, June 1996, September 1996, October 1996, November 1996 and December 1996]

Breathing monitors. [Potential legal action ?; ?; July 1990]

Brompheril. [Potential legal action ?; USA; December 1994]

Calpol. [Potential legal action ?; UK; August 1996]

Caverject powder. [Potential legal action ?; UK; April 1995]

Clozaril. [Potential legal action ?; USA; January 1991 and March 1991]

Cognex. [Potential legal action ?; USA; October 1993]

Collagen implants. [Legal action; USA; September 1991, March 1993 and June 1993]

Condoms. [Potential legal action ?; UK, USA, Thailand, Costa Rica, Bangladesh, Mexico and Brazil; February 1990, August 1993 and October 1993]

Conjugated estrogen tablets. [Potential legal action ?; USA; January 1990]

Corticosteroids. [Potential legal action?; UK; December 1994]

Corwin. [Potential legal action ?; UK; July 1990]

CU-7 contraceptive device. [Legal action; USA; April 1990]

Dalkon Shield. [Legal action; worldwide; March 1990 and October 1995]

Defibrillators. [Potential legal action ?; USA; August 1992, September 1993 and December 1993]

Denture adhesives. [Potential legal action; USA; February 1991 and August 1993]

Depo-Medrol. [Legal action; USA; October 1995]

Desipramine. [Potential legal action ?; USA; May 1990]

Diane 35. [Potential legal action ?; Germany; September 1994, October 1994 and December 1994]

Diethylstilboestrol. [Legal action; USA; July 1990, March 1991 and November 1991]

Diprivan. [Potential legal action ?; USA; August 1995]

Disposable tubing and syringes. [Potential legal action ?; USA; September 1991]

Enzygnost. [Potential legal action ?; Germany; November 1994]

Eucryl tooth powder. [Potential legal action ?; UK; January 1994]

Felbatol. [Potential legal action ?; USA; September and October 1994]

Femodene. [Legal action and potential legal action ?; UK and Germany; March 1995 , May 1995, June 1995, November 1995 and January 1996]

Fenoterol and a higher death rate among asthmatics. [Potential legal action ?; New Zealand; April 1990]

Fertility treatment. [Potential legal action ?; UK; May 1995]

Fialuridine. [Legal action; USA; January 1994]

Flucloxacillin and prolonged liver disease. [Potential legal action ?; Australia; January 1990]

Fluoride toothpaste and tablets. [Legal action; UK; May 1994 and December 1996]

Gammagard. [Potential legal action ?; Spain and Sweden; March 1994]

Gilfanan. [Potential legal action ?; Belgium, France and the Netherlands; January 1991 and February 1992]

Gravigard. [Legal action; UK and USA; April 1997]

H-BIG. [Potential legal action ?; USA; October 1992]

Halcion. [Legal action and potential legal action ?; USA, France, Netherlands, Spain and UK; September 1991, October 1991, November 1991, December 1991, January 1992, February 1992, April 1992, May 1992, August 1992, November 1992, June 1993, September 1993, January 1994, April 1994, May 1994, June 1994, October 1994, June 1995 and June 1996]

Heart valves. [Legal action; USA and UK; March 1990, May 1990, June 1990, October 1990, January 1991, February 1991, May 1991, August 1991, January 1992, February 1992, March 1992, April 1992, December 1992 and January 1993]

Herbal products. [Potential legal action ?; China; May 1996]

Hip replacement. [Legal action; UK; September 1995]

HIV testing kits. [Potential legal action ?; UK; May 1996]

Human growth hormone. [Legal action; UK; September 1995]

Human insulin. [Potential legal action ?; UK; September 1991]

Humidifiers. [Potential legal action?; USA; September 1993]

Imitrex. [Potential legal action ?; USA; September 1994]

Immravax. [Potential legal action ?; UK; September 1992]

Intal Fisonair. [Potential legal action ?; worldwide; December 1993]

Jaw implants. [Legal action; USA; March 1996]

Karvol. [Potential legal action ?; UK; December 1991]

Kidney Dialysis products. [Potential legal action?; USA; August 1993]

L-tryptophan. [Legal action; USA (including 2 UK claimants) and Japan; February 1990, April 1993, August 1990, September 1991, February 1992, September 1992, April 1993 and August 1993]

Lariam. [Potential legal action ?; UK; February 1996 and September 1996]

Laxatives. [Potential legal action ?; USA; November 1990]

Lederfen. [Potential legal action ?; UK; December 1991]

Lens care solution. [Potential legal action ?; USA; May 1995]

Linear accelerator and excess radiation dose. [Potential legal action ?; Spain; March 1991]

Logynon. [Legal action; UK; May 1995]

Losec. [Potential legal action ?; Germany; March 1994, August 1994]

Loxene. [Legal action; USA; July 1990]

Magnesium Hydroxide. [Potential legal action ?; UK; December 1993]

Manoplax. [Potential legal action ?; UK; June 1993 and July 1993]

Marvelon. [Legal action and potential legal action ?; UK, Germany and Norway; May 1995, November 1995, January 1996]

Measles vaccine. [Potential legal action; UK; January 1995]

Micturin. [Potential legal action ?; UK; August 1991 and September 1991]

Minocin. [Potential legal action ?; UK; August 1996]

Minulet. [Legal action and potential legal action ?; UK and Germany; May 1995, November 1995 and January 1996]

Myodil. [Legal action; UK; March 1990, August 1990, January 1993, June 1994 and August 1995]

Nurofen. [Potential legal action ?; UK; April 1990]

Omniflox. [Legal action; USA; March 1994]

Opren. [Legal action, UK; September 1990; September 1992]

Opticrom ophthalmic solution and bacterial contamination. [Potential legal action ?; USA; August 1990]

Oral contraceptives. [Potential legal action ?; ?; June 1990] See also Femodene, Logynon, Marvelon and Minulet.

Orcolon. [Potential legal action ?; USA; November 1991 and June 1992]

Organidin. [Potential legal action ?; USA; June 1993]

Pacemaker leads. [Legal action and potential legal action ?; USA and UK; February 1995 and February 1996]

Paracetamol syrup. [Potential legal action ?; Nigeria; September 1990 and October 1990]

Paracetamol and methionine. [Potential legal action ?; UK; December 1996]

Parlodel. [Potential legal action ?; USA; September 1994]

Pedicle screws. [Legal action; USA; August 1994 and February 1995]

Penicillin syrup. [Potential legal action ?; UK; February 1990]

Penile implants. [Legal action; USA; June 1994]

Plasma Plex. [Potential legal action?; USA; October 1996]

Pluserix-MMR. [Potential legal action ?; UK; September 1992]

Prozac. [Legal action; USA; August 1990, June 1991, August 1991, and January 1995]

Radiation machine. [Legal action; UK; October 1990]

Redux. [Potential legal action; USA; September 1996]

Ritodrine. [Potential legal action ?; UK; January 1993]

Rosiam. [Potential legal action ?; Europe; November 1993]

RU 486. [Potential legal action ?; France and USA; May 1991, July 1991 and July 1992]

Serevent. [Potential legal action ?; UK; June 1991]

Seldane. [Potential legal action ?; USA and UK; July 1992]

Septrin. [Potential legal action ?; UK; October 1994 and July 1995]

Shampoos and lotions containing carbyl for the treatment of head lice. [Potential legal action?; UK; December 1996]

Skin care and sunscreen products. [Potential legal action ? and legal action; Australia and UK; January 1991 and July 1995]

Sleep Monitors. [Legal action; USA; September 1993]

Sodium nitroprusside. [Legal action; USA; November 1990]

Sorivudine. [Potential legal action ?; Japan; September 1994]

Spinal dye. [Legal action, USA; September 1990]

Steroid treatment. [Potential legal action ?; UK; September 1995]

Sudafed. [Potential legal action ?; USA; March 1991, May 1991, July 1991 and September 1992]

Surgical devices (Trocar). [Potential legal action ?; USA; August 1992]

Tampons. [Potential legal action ?; UK and Australia; July 1992, May 1994 and March 1995]

Teflon jaw implants. [Legal action; USA; April 1993 and March 1995]

Triludan. [Potential legal action ?; USA and UK; July 1992]

Tylenol. [Legal action; USA; June 1991, November 1994, January 1995]

Unspecified product used in the treatment of asthma. [Legal action; USA; July 1990]

Unspecified oral antibiotics (Bristol-Myers Squibb). [Potential legal action; USA; May 1994]

Unspecified product used in the treatment of migraine. [Potential legal action ?; USA; October 1991]

Unspecified products (Abbott Laboratories). [Potential legal action ?; USA; April 1990]

Unspecified products (Quad Pharmaceuticals) [Potential legal action ?; USA; April 1990]

Usevir. [Potential legal action ?; Japan; December 1993]

Ventadisks. [Potential legal action ?; UK; September 1993]

Versed. [Potential legal action ?; USA; August 1991]

Vitamin Tonic. [Potential legal action ?; UK; August 1993]

Voltaren and liver problems. [Potential legal action ?; USA; December 1990]

Whooping cough vaccine. [Legal action; UK and Ireland; February 1991 and May 1993]

X-ray equipment. [Legal action; Spain; April 1993]

Zantac. [Potential legal action?; UK; August 1990]

Zentel. [Potential legal action ?; USA; May 1990]

Zofran. [Potential legal action ?; USA; November 1992]

Appendix III

Statutory Instruments Relating to Medicinal Products for Human Use, 1970 - 1997

1970
The Medicines Commission and Committees Regulations 1970. [S.I. No. 746; paragraph 1, schedule 1]
The Medicines (British Pharmacopoeia Commission) Order 1970. [S.I. No. 1256; section 4] *Amended by 1982/1335]*
The Medicines (Committee on Safety of Medicines) Order 1970. [S.I. No. 1257; section 4]
The Medicines (Veterinary Products Committee) Order 1970. [S.I. No. 1304; section 4]
1971
The Medicines (Standard Provisions for Licences and Certificates) Regulations 1971. [S.I. No. 972; section 47(1)] *Amended by 1972/1226, 1974/1523, 1977/675, 1977/1039, 1977/1053, 1983/1730, 1992/2846, 1992/3272, 1993/833 , 1993/2539 and 1994/103*
The Medicines (Applications for Product Licences and Clinical Trial and Animal Test Certificates) Regulations 1971. [S.I. No. 973; sections 18, 36 and 129(1)] *Amended by 1972/1201, 1975/681, 1977/1051, 1979/1760, 1983/1726, 1992/755 and 1993/2538*
The Medicines (Applications for Manufacturer's and Wholesale Dealer's Licences) Regulations 1971. [S.I. No. 974; sections 18 and 129(1)] *Amended by 1977/1052, 1978/1140, 1983/1725 and 1993/832*
The Medicines (First Appointed Day) Order 1971. [S.I. No. 1153; section 16(1)]
The Medicines (Exportation of Specified Products for Human Use) Order 1971. [S.I. No. 1198; section 48(1)] *Revoked by 1994/787*
The Medicines (Control of Substances for Manufacture) Order 1971. [S.I. No. 1200; section 105(a)] *Amended by 1994/787*
The Medicines (Surgical Materials) Order 1971. [S.I. No. 1267; section 104(1)] *Amended by 1994/3119*
The Medicines (Importation of Medicinal Products for Re-exportation) Order 1971. [S.I. No. 1326; section 13(2) and (3)] *Amended by 1977/640*
The Medicines (Exemption from Licences)(Food and Cosmetics) Order 1971. [S.I. No. 1410; section 15(1)] *Amended by 1973/2079*
The Medicines (Retail Pharmacists - Exemptions from Licensing Requirements) Order 1971. [S.I. No. 1445; section 15(3)]
The Medicines (Data Sheet)(Transitional) Regulations 1971. [S.I. No. 1446; sections 96(6) and 129(1)] *Revoked by 1972/2076*
The Medicines (Applications for Product Licence of Right and Clinical Trial and Animal Test Certificates of Right) Regulations 1971. [S.I. No. 1447; sections 18, 36 and 129(1)]
The Medicines (Applications for Manufacturer's and Wholesale Dealer's Licences of Right) Regulations 1971. [S.I. No. 1448; sections 18 and 129(1)] *Amended by 1977/1052*

The Medicines (Fees) Regulations 1971. [S.I. No. 1449; section 1(1) and (2) of the Medicines Act 1971] *Revoked by 1975/366*

The Medicines (Exemption from Licences)(Special and Transitional Cases) Order 1971. [S.I. No. 1450; sections 15(1) and 23(4)] *Amended by 1972/1200, 1978/1139, 1979/1585, 1989/1184 and 1989/2323*

1972

The Medicines (Exemption from Licences)(Wholesale Dealing) Order 1972. [S.I. No. 640; section 15(1)] *Amended by 1978/1139 and 1979/1585 ; revoked by 1989/2322*

The Medicines (Closing Date for Applications for Licences of Right) Order 1972. [S.I. No. 717; section 25(1)]

The Medicines Act 1968 (Commencement No. 1) Order 1972. [S.I. No. 788; section 136(3)]

The Medicines (Termination of Transitional Exemptions)(No. 1) Order 1972. [S.I. No. 1198; sections 17 and 37(3)]

The Medicines (Exemption from Licences)(Manufacture and Assembly Temporary Provisions) Order 1972. [S.I. No. 1199; sections 15(1) and 129(4)]

The Medicines (Exemption from Licences)(Special Cases and Miscellaneous Provisions) Order 1972. [S.I. No. 1200; sections 13(2), 15(1), 23(4), 35(8) and 129(4)] *Amended by 1974/498, 1978/1139, 1979/1585 and 1989/2323*

The Medicines (Applications for Product Licences and Clinical Trial and Animal Test Certificates) Amendment Regulations 1972. [S.I. No. 1201; sections 18, 36 and 129(1)]

The Medicines Act 1968 (Commencement No. 2) Order 1972. [S.I. No. 1225; section 136(3)]

The Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1972. [S.I. No. 1226; section 47(1)]

The Medicines (Data Sheet) Regulations 1972. [S.I. No. 2076; sections 96(6), 129(1) and (5)] *Amended by 1979/1760, 1981/1633, 1989/1183, 1994/3142 and 1996/2420*

1973

The Medicines (Extension to Antimicrobial Substances) Order 1973. [S.I. No. 367; section 105(1)(b) and (2)]

The Medicines (Hexachlorophane Prohibition) Order 1973. [S.I. No. 1120; section 62(1)] *Amended by 1974/2167; revoked by 1977/2127*

The Medicines Act 1968 (Commencement No. 3) Order 1973. [S.I. No. 1529; section 136(3)]

The Medicines (Pharmacies)(Applications for Registration and Fees) Regulations 1973. [S.I. No. 1822; sections 75(1), (2), 76(1), (2), (4) and (6)] *Amended by 1976/667, 1976/1961, 1977/511, 1977/2077, 1980/1806, 1981/1713, 1982/1719, 1983/1787, 1984/1886, 1985/1878, 1987/2099, 1988/2113, 1989/1985, 1990/2204, 1991/2605 , 1992/2939 1993/2902, 1994/2936, 1995/3029 and 1996/3054.*

The Medicines (Pharmacies)(Appointed Day) Order 1973. [S.I. No. 1849; section 69(3)]

The Medicines Act 1968 (Commencement No. 4) Order 1973. [S.I. No. 1851; sections 136(3) and (4)]

The Medicines (Exemption from Licences)(Foods and Cosmetics) Amendment Order 1973. [S.I. No. 2079; section 15(1)]

1974

The Medicines (Exemption from Licences)(Emergency Importation) Order 1974. [S.I. No. 316; section 13(2)]

The Medicines (Exemption from Licences)(Clinical Trials) Order 1974. [S.I. No. 498; sections 13(2), 15(1) and 35(8)(a)]

The Medicines (Interim Prescription Only)(No. 1) Order 1974. [S.I. No. 711; section 62(1)] *Amended by 1974/2167; revoked by 1977/2127*

The Medicines (Renewal Applications for Licences and Certificates) Regulations 1974. [S.I. No. 832; sections 18(1) and 36(1)] *Amended by 1977/180, 1982/1789 and 1992/755*

The Medicines (Phenacetin Prohibition) Order 1974. [S.I. No. 1082; section 62(1)(a)] *Amended by 1974/2167; revoked by 1977/2127*

The Medicines (Termination of Transitional Exemptions)(No. 2) Order 1974. [S.I. No. 1149; section 17]

The Medicines (Exemption from Licences)(Ingredients)Order 1974. [S.I. No. 1150; sections 13(2) and 15(1)]

The Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1974. [S.I. No. 1523; section 47(1)]

The Medicines (Interim Prescription Only)(No. 2) Order 1974. [S.I. No. 2167; section 62(1)(a)] *Revoked by 1977/2127*

1975

The Medicines (Advertising of Medicinal Products) Regulations 1975. [S.I. No. 298; section 95(1)(a) and (6)]

The Medicines (Fees) Regulations 1975. [S.I. No. 366; section 1(1) and (2) of the Medicines Act 1971] *Revoked by 1976/347*

The Medicines (Dental Filling Substances) Order 1975. [S.I. No. 533; section 104(1)] *Amended by 1994/3119*

The Medicines (Applications for Product Licences and Clinical Trial and Animal Test Certificates) Amendment Regulations 1975. [S.I. No. 681; sections 18(1) and 36(1)]

The Medicines (Termination of Transitional Exemption)(No. 3) Order 1975. [S.I. No. 761; section 17]

The Medicines (Exemption from Licences)(Wholesale Dealing in Confectionery)Order 1975. [S.I. No. 762; section 15(1)] *Amended by 1994/3144*

The Medicines (Committee on the Review of Medicines) Order 1975. [S.I. No. 1006; section 4(1)] *Revoked by 1992/606*

The Medicines (Medicines Act 1968 Amendment) Regulations 1975. [S.I. No. 1169; section 2(2) of the European Communities Act 1972]

The Medicines (Advertising of Medicinal Products)(No. 2). [S.I. No. 1326; section 95(3) and (6)] *Amended by 1979/1760 and 1994/1932*

The Medicines (Committee on Dental and Surgical Materials) Order 1975. [S.I. No. 1473; section 4(1)] *Amended by 1979/1535; revoked by 1994/3120*

The Medicines (Child Safety) Regulations 1975. [S.I. No. 2000; sections 87(1), 88(1), (2) and 91(2)] *Amended by 1976/1643, 1987/877,1994/1402 and 1994/3144*

1976

The Medicines Act 1968 (Commencement No. 5) Order 1976. [S.I. No. 74; section 136(3)]

The Medicines (Fees) Regulations 1976. [S.I. No. 347; section 1(1) and (2) of the Medicines Act 1971] *Amended by 1976/1145,1977/1056 and 1977/1374; revoked by 1978/1121*

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1976. [S.I. No. 667; sections 75(1), 76(1), (4) and (6)] *Amended by 1977/511; revoked by 1989/1985*

The Medicines (Specified Articles and Substances) Order 1976. [S.I. No. 968; section 104(1)]*Amended by 1994/3119*

The Medicines (Fees) Amendment Regulations 1976. [S.I. No. 1145; section 1(1) and (2) of the Medicines Act 1971] *Revoked by 1978/1121*

The Medicines (Child Safety) Amendment Regulations 1976. [S.I. No. 1643; sections 87(1), 88(1), (2) and 91(2)]

The Medicines (Labelling) Regulations 1976. [S.I. No. 1726; sections 85(1), 85(4), 86(1), 91(2) and (3)] *Amended by 1977/996, 1977/2168, 1978/1140, 1981/1791, 1983/1729, 1985/1558, 1989/1183 , 1992/3273, 1994/104 and 1994/3144*

The Medicines (Bal Jivan Chamcho Prohibition) Order 1976. [S.I. No. 1861; section 62(1)(a), (3), (4) and (7)]

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment (No. 2) Regulation 1976. [S.I. No. 1961; sections 75(1), 76(1), (2), and (6)] *Amended by 1977/511; revoked by 1989/1985*

The Medicines (Certificates of Analysis) Regulations 1976. [S.I. No. 1970; sections 112(9), 115(7) and Schedule 3, paragraphs 19(3), 20(1) and (2)] *Revoked by 1977/1399*

1977

The Medicines (Bal Jivan Chamcho Prohibition) Order 1977. [S.I. No. 172; section 62(1)(a), (3), (4) and (7)]

The Medicines (Renewal Applications for Licences and Certificates) Regulations 1977. [S.I. No. 180; section 18(1)]

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1977. [S.I. No. 511; section 76(2) and (6)] *Revoked by 1989/1985*

The Medicines (Importation of Medicinal Products for Re-exportation) Amendment Order 1977. [S.I. No. 640; section 13(2), (3) and 129(4)]

The Medicines (Bal Jivan Chamcho Prohibition) (No. 2) Order 1977. [S.I. No. 670; section 62(1)(a)] *Amended by 1997/856*

The Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1977. [S.I. No. 675; section 47(1)]

The Medicines (Labelling) Amendment Regulations 1977. [S.I. No. 996; sections 85(1), 85(4), 91(2) and (3)]

The Medicines (Manufacturer's Undertakings for Imported Products) Regulations 1977. [S.I. No. 1038; section 19(3)(b)] *Amended by 1992/2845 and 1994/3144*

The Medicines (Standard Provisions for Licences and Certificates) Amendment (No. 2) Regulations 1977. [S.I. No. 1039; section 47(1)]

The Medicines (Medicines Act 1968 Amendment) Regulations 1977. [S.I. No. 1050; section 2(2) of the European Communities Act 1972]

The Medicines (Applications for Product Licences and Clinical Trial and Animal Test Certificates) Amendment Regulations 1977. [S.I. No. 1051; sections 18(1) and 36(1)]

The Medicines (Applications for Manufacturer's and Wholesale Dealer's Licences) Amendment Regulations 1977. [S.I. No. 1052; section 18(1)]

The Medicines (Standard Provisions for Licences and Certificates) Amendment (No. 3) Regulations 1977. [S.I. No. 1053; section 47(1)]

The Medicines (Exemption from Licences)(Wholesale Dealing) Order 1977. [S.I. No. 1054; section 15(1)] *Amended by 1983/1728; revoked by 1989/2322*

The Medicines (Leaflets) Regulations 1977. [S.I. No. 1055; sections 86(1) and 91(2)] *Amended by 1992/3274, 1994/104 and 1994/3144*

The Medicines (Fees) Amendment Regulations 1977. [S.I. No. 1056; section 1(1) and (2) of the Medicines Act 1971] *Revoked by 1978/1121*

The Medicines Act 1968 (Commencement No. 6) Order 1977. [S.I. No. 1068; section 136(3)]

The Medicines (Fees) Amendment (No. 2) Regulations 1977. [S.I. No. 1374; section 1(1) and (2) of the Medicines Act 1971] *Revoked by 1978/1121*

The Medicines (Certificates of Analysis) Regulations 1977. [S.I. No. 1399; sections 112(9), 115(7) and Schedule 3, paragraphs 19(3), 20(1) and (2)]

The Medicines (Breathing Gases) Order 1977. [S.I. No. 1488; section 130(5)(c)]

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment (No. 2) Regulations 1977. [S.I. No. 2077; sections 75(1), 76(1), (2) and (6)] *Revoked by 1989/1985*

The Medicines (Pharmacy and General Sale)(Appointed Day) Order 1977. [S.I. No. 2126; section 52]

The Medicines (Prescription Only) Order 1977. [S.I. No. 2127; sections 58(1), (4), 59(1), 62 and 129(4)] *Amended by 1978/189, 1978/987, 1979/36, 1979/1040 and 1980/24; revoked by 1980/1921*

The Medicines Act 1968 (Commencement No. 7) Order 1977. [S.I. No. 2128; section 136(3) and (4)]

The Medicines (General Sale List) Order 1977. [S.I. No. 2129; section 51] *Amended by 1979/315 and 1980/7; revoked by 1980/1922*

The Medicines (Retail Sale or Supply of Herbal Medicines) Order 1977. [S.I. No. 2130; sections 56(3) and 57(1)]

The Medicines (Sale or Supply)(Miscellaneous Provisions) Regulations 1977. [S.I. No. 2132; sections 61, 66 and 67(6)] *Amended by 1978/989; revoked by 1980/1923*

The Medicines (Pharmacy and General Sale - Exemptions) Order 1977. [S.I. No. 2133; section 57(1)] *Amended by 1978/988; revoked by 1980/1924*

The Medicines (Labelling) Amendment (No. 2) Regulations 1977. [S.I. No. 2168; sections 85(1), 85(4), 91(2) and (3)]

1978

The Medicines (Fluted Bottles) Regulations 1978. [S.I. No. 40; sections 87(1), 91(2) and (3)] *Amended by 1994/3144*

The Medicines (Labelling and Advertising to the Public) Regulations 1978. [S.I. No. 41; sections 85(1), 86(1), 91(2), 95(1), (2), (3), (5), (6) and 129(5)] *Amended by 1994/1932*

The Medicines (Prescription Only) Amendment Order 1978. [S.I. No. 189; sections 58(1), (4)(a) and 129(4)] *Revoked by 1980/1921*

The Medicines (Labelling)(Special Transitional) Regulations 1978. [S.I. No. 190; sections 85(1) and 129(5)]

The Medicines (Prescription Only) Amendment (No. 2) Order 1978. [S.I. No. 987; sections 58(1), (4)(a) and 129(4)] *Revoked by 1980/1921*

The Medicines (Pharmacy and General Sale - Exemption) Amendment Order 1978. [S.I. No. 988; sections 57(1) and 129(4)] *Revoked by 1980/1924*

The Medicines (Sale or Supply)(Miscellaneous Provisions) Amendment Regulations 1978. [S.I. No. 989; sections 61 and 66(1)] *Revoked by 1980/1923*

The Medicines (Radioactive Substances) Order 1978. [S.I. No. 1004; section 104(1)]

The Medicines (Committee on Radiation from Radioactive Medicinal Products) Order 1978. [S.I. No. 1005; section 4(1)] *Revoked by 1984/1261*

The Medicines (Administration of Radioactive Substances) Regulations 1978. [S.I. No. 1006; section 2(2) of the European Communities Act 1972] *Revoked by 1992/606*

The Medicines (Advertising to Medical and Dental Practitioners) Regulations 1978. [S.I. No. 1020; sections 95 and 129(5)] *Revoked by 1994/1932*

The Medicines (Fees) Regulations 1978. [S.I. No. 1121; section 1(1) and (2) of the Medicines Act 1971] *Amended by 1979/899, 1980/16, 1980/1126, 1982/1121, 1983/1731, 1985/1231, 1987/1439; revoked by 1989/418*

The Medicines (Intra-Uterine Contraceptive Devices) (Appointed Day) Order 1978. [S.I. No. 1138; section 16(1)]

The Medicines (Intra-Uterine Contraceptive Devices)(Amendment to Exemption from Licences) Order 1978. [S.I. No. 1139; sections 13(2), 15(1), 23(4), 35(8) and 129(4)]

The Medicines (Licensing of Intra-Uterine Contraceptive Devices) (Miscellaneous Amendments) Regulations 1978. [S.I. No. 1140; sections 18, 85(1), 85(4), 86(1), 91(2), (3) and 129(1)]

The Medicines (Collection and Delivery Arrangements Exemption) Order 1978. [S.I. No. 1421; section 57(1)]

The Medicines (Exemption from Licences)(Importation) Order 1978. [S.I. No. 1461; sections 13(2), (3), 15(1) and (2)] *Revoked by 1984/673*

1979

The Medicines (Prescription Only) Amendment Order 1979. [S.I. No. 36; sections 58(1), (4)(a) and 129(4)] *Revoked by 1980/1921*

The Medicines (General Sale List) Amendment Order 1979. [S.I. No. 315; sections 51 and 129(4)] *Revoked by 1980/1922*

The Medicines (Chloroform Prohibition) Order 1979. [S.I. No. 382; section 62] *Amended by 1980/263 and 1989/1184*

The Medicines (Fees) Amendment Regulations 1979. [S.I. No. 899; section 1(1) and (2) of the Medicines Act 1971] *Revoked by 1989/418*

The Medicines (Prescription Only) Amendment (No. 2) Order 1979. [S.I. No. 1040; sections 58(1) and 129(4)] *Revoked by 1980/1921*

The Medicines (Exemption from Licences)(Assembly) Order 1979. [S.I. No. 1114; section 15(1) and 15(2)]

The Medicines (Phenacetin Prohibition) Order 1979. [S.I. No. 1181; section 62] *Revoked by 1996/3269*

The Medicines (Committee on Dental and Surgical Materials) Amendment Order 1979. [S.I. No. 1535; sections 4 and 129(4)] *Revoked by 1994/3120*

The Medicines (Contact Lens Fluids and Other Substances) (Appointed Day) Order 1979. [S.I. No. 1539; section 16(1)]

The Medicines (Contact Lens Fluids and Other Substances) (Exemption from Licences) Order 1979. [S.I. No. 1585; sections 13(2), 15(1), (2), 23(4), 35(8) and 129(4)] *Amended by 1979/1745*

The Medicines (Contact Lens Fluids and Other Substances)(Exemption from Licences)Amendment Order 1979. [S.I. No. 1745; sections 15(1), (2) and 129(4)]

The Medicines (Contact Lens Fluids and Other Substances) (Labelling) Regulations 1979. [S.I. No. 1759; sections 85(1), 86(1), 91(2), (3) and 129(5)] *Amended by 1981/1689*

The Medicines (Contact Lens Fluids and Other Substances) (Advertising and Miscellaneous Amendments) Regulations 1979. [S.I. No. 1760; sections 18, 36, 95, 96(6), 129(1) and (5)]

1980

The Medicines (General Sale List) Amendment Order 1980. [S.I. No. 7; sections 51 and 129(4)] *Revoked by 1980/1922*

The Medicines (Fees) Amendment Regulations 1980. [S.I. No. 16; section 1(1) and (2) of the Medicines Act 1971] *Revoked by 1989/418*

The Medicines (Prescription Only) Amendment Order 1980. [S.I. No. 24; sections 58(1), (4)(a) and 129(4)] *Revoked by 1980/1921*

The Medicines (Chloroform Prohibition) Amendment Order 1980. [S.I. No. 263; sections 62 and 129(4)]

The Medicines (Fees) Amendment (No. 2) Regulations 1980. [S.I. No. 1126; section 1(1) and (2) of the Medicines Act 1971] *Revoked by 1989/418*

The Medicines (Intra-Uterine Contraceptive Devices) (Termination of Transitional Exemptions) Order 1980. [S.I. No. 1467; section 17]

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1980. [S.I. No. 1806; sections 75(1), 76(1), (2) and (6)]

The Medicines (Prescription Only) Order 1980. [S.I. No. 1921; sections 58(1), (4)(a), 59 and 129(4)] *Amended by 1981/80, 1982/29, 1982/1596, 1982/1801, 1983/341 and 1983/957; revoked by 1983/1212*

The Medicines (General Sale List) Order 1980. [S.I. No. 1922; sections 51 and 129(4)] *Amended by 1982/26 ; revoked by 1984/769*

The Medicines (Sale or Supply)(Miscellaneous Provisions) Regulations 1980. [S.I. No. 1923; sections 53(4), 61, 66(1), 67(6) and 129(1)] *Amended by 1982/28, 1990/1124 , 1992/2938, 1994/2411 ,1994/3144, 1995/3215, 1997/1831 and 1997/2045*

The Medicines (Pharmacy and General Sale - Exemption) Order 1980. [S.I. No. 1924; sections 57(1), (2) and 129(4)] *Amended by 1982/27 , 1989/1852, 1994/3144 and 1997/1350*

1981

The Medicines (Prescription Only) Amendment Order 1981. [S.I. No. 80; sections 58(1), (4)(a) and 129(4)] *Revoked by 1983/1212*

The Medicines (Exemption from Licences)(Clinical Trials) Order 1981. [S.I. No. 164; sections 15(1), (2), 35(8)(a) and (9)] *Amended by 1995/2808; revoked by 1995/2809*

The Medicines (Data Sheet) Amendment Regulations 1981. [S.I. No. 1633; sections 96(6) and 129(1)]

The Medicines (Contact Lens Fluids and Other Substances)(Labelling) Amendment Regulations 1981. [S.I. No. 1689; sections 85(1), 86(1), 91(2), (3) and 129(5)]

The Medicines (Contact Lens Fluids and Other Substances) (Termination of Transitional Exemptions) Order 1981. [S.I. No. 1690; section 17]

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1981. [S.I. No. 1713; sections 75(1), 76(1), (2) and (6)] *Revoked by 1989/1985*

The Medicines (Labelling) Amendment Regulations 1981. [S.I. No. 1791; sections 85(1) and 129(5)]

1982

The Medicines (General Sale List) Amendment Order 1982. [S.I. No. 26; sections 51 and 129(4)] *Revoked by 1984/769*

The Medicines (Pharmacy and General Sale - Exemption) Amendment Order 1982. [S.I. No. 27; sections 57(1), (2) and 129(4)]

The Medicines (Sale or Supply)(Miscellaneous Provisions) Amendment Regulations 1982. [S.I. No. 28; sections 53(4) and 129(1)]

The Medicines (Prescription Only) Amendment Order 1982. [S.I. No. 29; sections 58(1), (4)(a), 59 and 129(4)] *Revoked by 1983/1212*

The Medicines (Control of Substances for Manufacture) Order 1982. [S.I. No. 425; section 105(a)]

The Medicines (Fees) Amendment Regulations 1982. [S.I. No. 1121; section 1(1) and (2) of the Medicines Act 1971] *Revoked by 1989/418*

The Medicines (British Pharmacopoeia Commission) Amendment Order 1982. [S.I. No. 1335; sections 4 and 129(4)]

The Medicines (Prescription Only) Amendment (No. 2) Order 1982. [S.I. No. 1596; sections 58(1), (4)(a) and 129(4)] *Revoked by 1983/1212*

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1982. [S.I. No. 1719; sections 75(1), 76(1), (2) and (6)] *Revoked by 1989/1985*

The Medicines (Renewal Applications for Licences and Certificates) Amendment Regulations 1982. [S.I. No. 1789; sections 18(1) and 36(1)]

The Medicines (Prescription Only) Amendment (No. 3) Order 1982. [S.I. No. 1801; sections 58(1), (4)(a) and 129(4)] *Revoked by 1983/1212*

1983

The Medicines (Prescription Only) Amendment Order 1983. [S.I. No. 341; sections 58(1), (4) and 129(4)] *Revoked by 1983/1212*

The Medicines (Prescription Only) Amendment (No. 2) Order 1983. [S.I. No. 957; sections 58(1) and 129(4)] *Revoked by 1983/1212*

The Medicines (Products other than Veterinary Drugs)(Prescription Only) Order 1983. [S.I. No. 1212; sections 58(1), (4), 59 and 129(4)] *Amended by 1984/756, 1986/586 , 1987/674, 1987/1250, 1988/2017, 1989/1852, 1991/962, 1992/1534, 1992/2937, 1993/1890, 1993/3256, 1994/558, 1994/3016, 1994/3050 ,1995/1384, 1995/3174, 1996/1514 and 1996/3193. Revoked by 1997/1830.*

The Medicines (Medicines Act 1968 Amendment) Regulations 1983. [S.I. No. 1724; section 2(2) of the European Communities Act 1972]

The Medicines (Applications for Manufacturer's and Wholesale Dealer's Licences) Amendment Regulations 1983. [S.I. No. 1725; section 18(1)]

The Medicines (Applications for Product Licences and Clinical Trial and Animal Test Certificates) Amendment Regulations 1983. [S.I. No. 1726; section 18(1)]

The Medicines (Exemption from Licences)(Wholesale Dealing) Amendment Order 1983. [S.I. No. 1728; section 15(1)] *Revoked by 1989/2322*

The Medicines [Labelling] Amendment Regulations 1983. [S.I. No. 1729; sections 85(1), 85(4) and 91(3)]

The Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1983. [S.I. No. 1730; section 47(1)]

The Medicines (Fees) Amendment Regulations 1983. [S.I. 1731; section 1(1) and (2) of the Medicines Act 1971] *Revoked by 1989/418*

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1983. [S.I. No. 1787; sections 75(1), 76(1), (2) and (6)] *Revoked by 1989/1985*

1984

The Medicines (Cyanogenetic Substances) Order 1984. [S.I. No. 187; section 104(1)]

The Medicines (Exemption from Licences)(Importation) Order 1984. [S.I. No. 673; sections 13(2), (3), 15(1) and (2)]

The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment Order 1984. [S.I. No. 756; sections 58(1), (4), and 129(4)] *Revoked by 1997/1830*

The Medicines (Products other than Veterinary Drugs)(General Sale List) Order 1984. [S.I. No. 769; sections 51 and 129(4)] *Amended by 1985/1540, 1987/910, 1989/969, 1990/1129 , 1992/1535, 1994/2410, 1995/3216 and 1997/2043*

The Medicines (Committee on Radiation from Radioactive Medicinal Products)(Revocation) Order 1984. [S.I. No. 1261; sections 4(1) and 129(4)]

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1984. [S.I. No. 1886; sections 75(1), 76(1), (2) and (6)] *Revoked by 1989/1985*

1985

The Medicines (Fees) Amendment Regulations 1985. [S.I. No. 1231; section 1(1) and (2) of the Medicines Act 1971] *Revoked by 1989/418*

The Vaccine Damage Payments Act 1979 Statutory Sum Order 1985. [S.I. No. 1249; section 1(4A) of the Vaccine Damage Payments Act 1979] *Revoked by 1991/939*

The Medicines (Control of Substances for Manufacture) Order 1985. [S.I. No. 1403; section 105(1)(a)] *Amended by 1994/787*

The Medicines (Control of Substances for Manufacture)(Appointed Day) Order 1985. [S.I. No. 1539; section 16(1)]

The Medicines (Products other than Veterinary Drugs)(General Sale List) Amendment Order 1985. [S.I. No. 1540; sections 51 and 129(4)]

The Medicines (Labelling) Amendment Regulations 1985. [S.I. No. 1558; sections 85(1), 91(3) and 129(5)]

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1985. [S.I. No. 1878; sections 75(1), 76(1), (2) and (6)] *Revoked by 1989/1985*

1986

The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment Order 1986. [S.I. No. 586; sections 58(1), (4), and 129(4)] *Revoked by 1997/1830*

The Medicines Act 1968 (Hearings by Persons Appointed) (Scotland) Rules 1986. [S.I. No. 1700; section 11 of the Tribunals and Inquiries Act 1971]

The Medicines Act 1968 (Hearings by Persons Appointed) Rules 1986. [S.I. No. 1761; section 11 of the Tribunals and Inquiries Act 1971]

1987

The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment Order 1987. [S.I. No. 674; sections 58(1), (4), (5) and 129(4)] *Revoked by 1997/1830*

The Medicines (Child Safety) Amendment Regulations 1987. [S.I. No. 877; sections 87(1) and 129(5)]

The Medicines (Products other than Veterinary Drugs)(General Sale List) Amendment Order 1987. [S.I. No. 910; sections 51 and 129(4)]

The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment (No. 2) Order 1987. [S.I. No. 1250; sections 58(1), (4)(a), and 129(4)] *Revoked by 1997/1830*

The Medicines (Fees) Amendment Regulations 1987. [S.I. No. 1439; section 1(1) and (2) of the Medicines Act 1971] *Revoked by 1989/418*

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1987. [S.I. No. 2099; sections 75(1), 76(1), (6), 129(2), (5) and 132(1)] *Revoked by 1989/1985*

1988

The Medicines (Products other than veterinary drugs)(Prescription Only) Amendment Order 1988. [S.I. No. 2017; sections 58(1), (4), (5), and 129(4)] *Revoked by 1997/1830.*

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1988. [S.I. No. 2113; sections 75(1), 76(1), (6), 129(2), (5) and 132(1)] *Revoked by 1989/1985*

1989

The Medicines (Commencement No. 8) Order 1989. [S.I. No. 192; section 136(3)]

The Medicines (Fees Relating to Medicinal Products for Human Use) Regulations 1989. [S.I. No. 418; section 1(1) and (2) of the Medicines Act 1971] *Amended by 1990/210 and 1990/2326; revoked by 1991/1474*

The Medicines (Fixing of Fees Relating to Medicinal Products for Human Use) Order 1989. [S.I. No. 684; section 1(1) of the Medicines Act 1971] *Amended by 1995/871*

The Medicines (Products other than Veterinary Drugs)(General Sale List) Amendment Order 1989. [S.I. No. 969; sections 51 and 129(4)]

The Medicines (Data Sheet and Labelling) Amendment Regulations 1989. [S.I. No. 1183; sections 85(1), 91(3), 96(6), 129(1), (5) and 132(1)]

The Medicines (Exemption from Licences)(Special and Transitional Cases) Amendment Order 1989. [S.I. No. 1184; sections 15(1), (2) and 129(4)]

The Medicines (Prescription Only, Pharmacy and General Sale) Amendment Order 1989. [S.I. No. 1852; sections 1, 57(1), (2), 58(1), (4)(a), 129(4) and 132(1)] *Amended by 1989/1852*

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1989. [S.I. No. 1985; sections 1(1)(a), 75(1), 76(1), (2), (6), 129(2), (5) and 132(1)] *Revoked by 1990/2204*

The Medicines (Exemption from Licences)(Wholesale Dealing) Order 1989. [S.I. No. 2322; sections 15(1) and 129(4)] *Revoked 1990/566*

The Medicines (Exemption from Licences)(Special and Transitional Cases)(Amendment) Order 1989. [S.I. No. 2323; sections 15(1) and 129(4)]

1990

The Medicines (Fees Relating to Medicinal Products for Human Use) Amendment Regulations 1990. [S.I. No. 210; section 1(1) of the Medicines Act 1971] *Revoked by 1991/1474*

The Medicines (Exemption from Licences)(Wholesale Dealing) Regulations 1990. [S.I. No. 566; section 15(1) and 129(4)] *Amended by 1994/3144*

The Medicines (Sale or Supply)(Miscellaneous Provisions) Amendment Regulations 1990. [S.I. No. 1124; sections 1(1), 53(4), 129(1), (5) and 132(1)]

The Medicines (Products other than Veterinary Drugs)(General Sale List) Amendment Order 1990. [S.I. No. 1129; sections 1(2), 51, 129(4)and 132(1)]

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1990. [S.I. No. 2204; sections 1(1)(a), 75(1), 76(1), (2), (6), 129(2), (5) and 132(1)] *Revoked by 1991/2605*

The Medicines (Fees Relating to Medicinal Products for Human Use) Amendment (No. 2) Regulations 1990. [S.I. No. 2326; section 1(1) of the Medicines Act 1971] *Revoked by 1991/1474*

1991

The Vaccine Damage Payments Act 1979 Statutory Sum Order 1991. [S.I. No. 939; section 1(4A) of the Vaccine Damage Payments Act 1979]

The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment Order 1991. [S.I. No. 962; sections 1(2), 58(1), 129(4) and 132(1)] *Revoked by 1997/1830*

The Medicines (Products for Human Use - Fees) Regulations 1991. [S.I. No. 1474; section 1(1) and (2) of the Medicines Act 1971] *Amended by 1992/756 and 1994/696; revoked by 1995/1116*

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1991. [S.I. No. 2605; sections 1(1)(a), 75(1), 76(1), (2), (6), 129(5) and 132(1)] *Revoked by 1992/2939*

1992

The Medicines (Medicines Act 1968)(Amendment) Regulations 1992. [S.I. No. 604; section 2(2) of the European Communities Act 1972]

The Medicines (Application to Radiopharmaceutical - Associated Products) Regulations 1992. [S.I. No. 605; section 2(2) of the European Communities Act 1972]

The Medicines (Committee on the Review of Medicines)(Revocation) Order 1992. [S.I. No. 606; sections 4(1) and 129(4)]

The Medicines (Applications for Grant and Renewal of Licences)(Miscellaneous Amendments) Regulations 1992. [S.I. No. 755; sections 18 and 129(1)]

The Medicines (Products for Human Use - Fees) Amendment Regulations 1992. [S.I. No. 756; section 1(1) and (2) of the Medicines Act 1971] *Revoked by 1995/1116*

The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment Order 1992. [S.I. No. 1534; sections 1(2), 58(1), 129(4) and 132(1)] *Revoked by 1997/1830.*

The Medicines (Products other than Veterinary Drugs)(General Sale List) Amendment Order 1992. [S.I. No. 1535; sections 1(2), 51, 129(4)and 132(1)]

The Medicines (Exemptions from Licensing)(Radiopharmaceuticals) Order 1992. [S.I. No. 2844; section 15(1)]

The Medicines (Manufacturer's Undertakings for Imported Products) Amendment Regulations 1992. [S.I. No. 2845; sections 19(3)(b), 129(1) and (5)]

The Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1992. [S.I. No. 2846; section 47(1)]

The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment (No. 2) Order 1992. [S.I. No. 2937; sections 58(1), (4) and 129(4)] *Revoked by 1997/1830*

The Medicines (Sale or Supply)(Miscellaneous Provisions) Amendment Regulations 1992. [S.I. No. 2938; sections 61, 129(1) and (5)]

The Medicines (Pharmacies)(Applications) for Registration and Fees) Amendment Regulations 1992. [S.I. No. 2939; sections 75(1), 76(1), (2), (6) and 129(5)]

The Active Implantable Medical Devices Regulations 1992. [S.I. No. 3146; sections 11 and 27(2)(b)of the Consumer Protection Act 1987] *Amended by 1995/1671*

The Medicines (Medicines Act 1968)(Amendment)(No. 2) Regulations 1992. [S.I. No. 3271; section 2(2) of the European Communities Act 1972]

The Medicines (Standard Provisions for Licences and Certificates) Amendment (No. 2) Regulations 1992. [S.I. No. 3272; section 47(1)]

The Medicines (Labelling) Amendment Regulations 1992. [S.I. No. 3273; sections 85(1) and 91(3)]

The Medicines (Leaflets) Amendment Regulations 1992. [S.I. No. 3274; sections 86(1) and 91(3)]

1993

The Medicines (Application for Manufacturer's and Wholesale Dealer's Licences) Amendment Regulations 1993. [S.I. No. 832; sections 18 and 129(1)]

The Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1993. [S.I. No. 833; section 47(1)]

The Medicines Act 1968 (Amendment) Regulations 1993. [S.I. No. 834; section 2(2) of the European Communities Act 1972]

The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment Order 1993. [S.I. No. 1890; sections 58(1), (4)(a) and 129(4)] *Revoked by 1997/1830*

The Medicines (Applications for Grant of Product Licences - Products for Human Use) Regulations 1993. [S.I. No. 2538; sections 18, 129(1), (5) and 132(1)] *Amended by 1994/3144*

The Medicines (Standard Provisions for Licences and Certificates) Amendment (No. 2) Regulations 1993. [S.I. No. 2539; sections 47(1) and 129(5)]

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1993. [S.I. No. 2902; sections 75(1), 76(1), (2), (6) and 129(5)] *Revoked by 1994/2936.*

The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment (No. 2) Order 1993 [S.I. No. 3256; sections 58(1), (4), (5), 129(4) and 132(1)] *Revoked by 1997/1830*

1994

The Medicines Act 1968 (Amendment) Regulations 1994. [S.I. No. 101; section 2(2) of the European Communities Act 1972]

The Medicines (Advisory Board on the Registration of Homeopathic Products) Order 1994. [S.I. No. 102; section 4] *Revoked by 1995/309*

The Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1994. [S.I. No. 103; sections 47(1) and 129(5)]

The Medicines (Labelling and Leaflets) Amendment Regulations 1994. [S.I. No. 104; sections 85(1), 86(1) and 91(3)]

The Medicines (Homeopathic Medicinal Products for Human Use) Regulations 1994. [S.I. No. 105; section 2(2) of the European Communities Act 1972] *Amended by 1994/899 , 1995/541 and 1996/482*

The Medicines Act 1968 (Amendment)(No. 2) 1994. [S.I. No. 276; section 2(2) of the European Communities Act 1972]

The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment Order 1994. [S.I. No. 558; sections 58(1), (4), (5) and 129(4)] *Revoked by 1997/1830*

The Medicines (Products for Human Use - Fees) Amendment Regulations 1994. [S.I. No. 696; section 1(1) and (2) of the Medicines Act 1971] *Revoked by 1995/1116*

The Medicines (Control of Substances for Manufacture and Exportation of Specified Products for Human Use) Amendment Order 1994. [S.I. No. 787; sections 105(1)(a) and 129(4)]

The Medicines (Homeopathic Medicinal Products for Human Use) Amendment Regulations 1994. [S.I. No. 899; section 2(2) of the European Communities Act 1972]]

The Medicines (Child Safety) Amendment Regulations 1994. [S.I. No. 1402; sections 87(1), 91(3) and 129(5)]

The Medicines (Advertising) Regulations 1994. [S.I. No. 1932; sections 61, 66(1)(i), (j), 95(1), (2), (3), (4), (5), (6) and 129(5)] *Amended by 1994/3144 and 1996//1552*

The Medicines (Monitoring of Advertising) Regulations 1994. [S.I. No. 1933; section 2(2) of the European Communities Act 1972]

The Medicinal Products: Prescription by Nurses etc. Act 1992 (Commencement No. 1) Order 1994. [S.I. No. 2408; section 6(2) of the Prescription by Nurses etc. Act 1992]

The Medicines (Pharmacy and General Sale - Exemption) Amendment Order 1994. [S.I. No. 2409; sections 57(1), (2) and 129(4)]

The Medicines (Products other than Veterinary Drugs)(General Sale List) Amendment Order 1994. [S.I. No. 2410; sections 51 and 129(4)]

The Medicines (Sale or Supply)(Miscellaneous Provisions) Amendment Regulations 1994. [S.I. No. 2411; sections 53(4), 129(1) and (5)]

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1994. [S.I. No. 2936; sections 75(1), 76(1), (2), (6) and 129(5)] *Revoked by 1995/3029*

The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment (No. 2) Order 1994. [S.I. No. 3016; sections 58(1), (4), (5) and 129(4)] *Revoked by 1997/1830*

The Medical Devices Regulations 1994. [S.I. No. 3017; sections 11 and 27(2) of the Consumer Protection Act 1987]

The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment (No. 3) Order 1994. [S.I. No. 3050; sections 58(1) and 129(4)] *Revoked by 1997/1830*

The Medicines (Consequential Amendments - Medicines) Regulations 1994. [S.I. No. 3119; section 2(2) of the European Communities Act 1972]

The Medicines (Committee on Dental and Surgical Materials)(Revocation) Order 1994. [S.I. No. 3120; sections 4 and 129(4)]

The Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994. [S.I. No. 3144; section 2(2) of the European Communities Act 1972]]

1995
The Medicines (Advisory Board on the Registration of Homeopathic Products) Order 1995. [S.I. No. 309; sections 4 and 129(4)]
The Medical Devices (Consultation Requirements)(Fees) Regulations 1995. [S.I. No. 449; sections 56(1) and (2) of the Finance Act 1973] *Amended by 1996/622*
The Medicines (Homeopathic Medicinal Products for Human Use) Amendment Regulations 1995. [S.I. No. 541; section 2(2) of the European Communities Act 1972]
The Medicines (Fixing of Fees relating to Medicinal Products for Human Use) Amendment Order 1995. [S.I. No. 871; section 1(1) of the Medicines Act 1971 and section 102 of the Finance (No. 2) Act 1987]
The Medicines (Products for Human Use - Fees) Regulations 1995. [S.I. No. 1116; section 1(1) and (2) of the Medicines Act 1971] *Amended by 1996/683*
The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment Order 1995. [S.I. No. 1384; sections 58(1), (4), (5) and 129(4)] *Revoked by 1997/1830*
The Active Implantable Medical Devices (Amendment and Transitional Provisions) Regulations 1995. [S.I. No. 1671; section 11 of the Consumer Protection Act 1987]
The Medicines Act (Amendment) Regulations 1995. [S.I. No. 2321; section 2(2) of the European Communities Act 1972]
The Medical Devices Fees Regulations 1995. [S.I. No. 2487; section 56(1) and (2) of the Finance Act 1973] *Amended by 1997/694*
The Medicines (Exemption from Licences)(Clinical Trials) Order 1995. [S.I. No. 2808; Sections 15(1) and 129(4)
The Medicines (Exemption from Licences and Certificates)(Clinical Trials) Order 1995. [S.I. No. 2809; sections 35(8)(a) and 129(4)]
The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1995. [S.I. No. 3029; sections 75(1), 76(1), (2), (6) and 129(5)]
The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment (No. 2) Order 1995. [S.I. No. 3174; sections 58(1), (4), (5) and 129(4)] *Revoked by 1997/1830*
The Medicines (Sale or Supply)(Miscellaneous Provisions) Amendment Regulations 1995. [S.I. No. 3215; sections 53(4), 129(1) and (5)]
The Medicines (Products other than Veterinary Drugs)(General Sale List) Amendment Order 1995. [S.I. No. 3216; sections 51 and 129(4)]
1996
The Medicines (Homeopathic Medicinal Products for Human Use) Amendment Regulations 1996. [S.I. No. 482; section 2(2) of the European Communities Act 1972]
The Medical Devices (Consultation Requirements)(Fees) Amendment Regulations 1996. [S.I. No. 622; section 56(1) and (2) of the Finance Act 1973]

The Medicines (Products for Human Use - Fees) Amendment Regulations 1996. [S.I. No. 683; section 1(1) and (2) of the Medicines Act 1971]

The Medicinal Products: Prescription by Nurses etc. Act 1992 (Commencement No. 2) Order 1996. [S.I. No. 1505; section 6(2) of the Prescription by Nurses etc. Act 1992]

The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment Order 1996. [S.I. No. 1514; sections 58(1) and 129(4)] *Revoked by 1997/1830*

The Medicines (Advertising) Amendment Regulations 1996. [S.I. No. 1552; sections 95(1)(b) and 129(4)]

The Medicines (Data Sheet) Amendment Regulations 1996. [S.I. No. 2420; sections 96(6), 129(1) and (5)]

The Medicines (Pharmacies)(Applications for Registration and Fees) Amendment Regulations 1996. [S.I. No. 3054; sections 75(1), 76(1), (2), (6) and 129(5)]

The Medicines (Products other than Veterinary Drugs)(Prescription Only) Amendment (No. 2) Order 1996. [S.I. No. 3193; sections 58(1) and 129(4)] *Revoked by 1997/1830*

The Medicines (Phenacetin Prohibition)(Revocation) Order 1996. [S.I. No. 3269; sections 62 and 129(4)]

1997

The Medical Devices Fees (Amendment) Regulations 1997. [S.I. No. 694; section 56(1) and (2) of the Finance Act 1973.]

The Medicines (Bal Jivan Chamcho Prohibition)(No. 2) Amendment Order 1997. [S.I. No. 856; sections 62(1)(a) and 129(4)]

The Medicines (Pharmacy and General Sale - Exemption)(Amendment) Order 1997. [S.I. No. 1350; sections 57(1), (2) and 129(4)]

The Prescription Only Medicines (Human Use) Order 1997. [S.I. No. 1830; sections 58(1), (4) and (5), 59(1) and 129(4)] *Amended by 1997/2044*

The Medicines (Sale or Supply)(Miscellaneous Provisions) Amendment Regulations 1997. [S.I. No. 1831; sections 66(1)(I) and 129(1)]

The Medicines (Products other than Veterinary Drugs)(General Sale List) Amendment Order 1997. [S.I. No. 2043; sections51 and 129(4)]

The Prescription Only Medicines (Human Use) Amendment Order 1997. [S.I. No. 2044; sections 58(1), (4) and (5) and 129(4)]

The Medicines (Sale or Supply)(Miscellaneous Provisions) Amendment (No. 2). [S.I. No. 2045; sections 53(4) and 129(1) and (5)]

Appendix IV

European Directives, Decisions, Regulations, Recommendations, Opinions and COM Documents Relating to Medicinal Products and Medical Devices for Human Use 1965 - 1997

1965

- Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. [O.J. No. 22, 9.2.65, p369/65]

The Medicines (Medicines Act 1968 Amendment) Regulations 1977. [S.I. No. 1050]; The Medicines (Medicines Act 1968)(Amendment) Regulations 1992. [S.I. No. 604]; The Medicines for Human Use (Marketing Authorizations Etc.) Regulations 1994. [S.I. No. 3144]

1974

- Opinion on the

  'Amendment to the proposal for a Council Directive on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products'.

  'Amendment to the proposal for a Council Directive on the approximation of the laws of the Member States relating to publicity for proprietary medicinal products and to package leaflets'.

  'Amendment to the proposal for a Council Directive on the approximation of the laws of the Member States relating to matter which may be added to proprietary medicinal products for colouring purposes'. [O.J. No. C116, 30.9.74, p24]

1975

- Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of the Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products. [O.J. No. L147, 9.6.75, p1]

The Medicines for Human Use (Marketing Authorizations Etc.) Regulations 1994. [S.I. No. 3144]

- Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. [O.J. No. L147, 9.6.75, p13]

The Medicines (Medicines Act 1968 Amendment) Regulations 1977. [S.I. No. 1050]; The Medicines (Medicines Act 1968)(Amendment) Regulations 1992. [S.I. No. 604]; The Medicines for Human Use (Marketing Authorizations Etc.) Regulations 1994. [S.I. No. 3144]

- Council Decision 75/320/EEC of 20 May 1975 setting up a Pharmaceutical Committee. [O.J. No. L147, 9.6.75, p23]

1978

- Council Directive 78/25/EEC of 12 December 1977 on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products. [O.J. No. L11, 14.1.78, p18]]

- Opinion on the proposal for a Council Directive amending Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. [O.J. No. C18, 23.1.78, p11]

- Council Directive of 2 May 1978 amending Second Directive 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. [78/420/EEC; O.J. No. L123, 11.5.78, p26]

1979
• First Commission report to the Council on the functioning of the Committee for Proprietary Medicinal Products. [COM (79) 59; 22.2.79]
1980
• Second Commission report to the Commission on the functioning of the Committee for Proprietary Medicinal Products. [COM(80) 149; 31.3.80]
• Opinion on the proposal for a Council Directive amending Council Directive 78/25/EEC on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products. [O.J. No. C113, 7.5.80, p36]
• Opinion on the proposal for a Council Directive amending Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. [O.J. No. C348, 31.12.80, p40]
1981
• Council Directive of 24 June 1981 amending Council Directive 78/25/EEC on the approximation of the rules of the Member States relating to the colouring matters which may be added to medicinal products. [81/464/EEC; O.J. No. L183, 4.7.81, p33]
• Third Commission report to the Council on the functioning of the Committee for Proprietary Medicinal Products. [COM(81) 363; 13.7.81]
• Opinion on the proposal for a Council Directive amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. [O.J. No. C189, 30.7.81, p39]
1982
• Fourth Commission report to the Council on the functioning of the Committee for Proprietary Medicinal Products. [COM(82) 787; 3.12.82]
1983
• Council Directive 83/189/EEC of 28 March 1983 laying down a procedure for the provision of information in the field of technical standards and regulations. [O.J. No. L109, 26.4.83, p8]
• Council Directive 83/570/EEC of 26 October 1983 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. [O.J. No. L332, 28.11.83, p1]
• Council Recommendation of 26 October 1983 concerning tests relating to the placing on the market of proprietary medicinal products, [83/571/EEC; O.J. No. L332, 28.11.83, p11]

1984

- Proposal for a Council Directive on the approximation of national measures relating to the placing on the market of high technology medicinal products, particularly those derived from biotechnology.

  Proposal for a Council Directive amending Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products.

  Proposal for a Council Directive amending Directive 81/852/EEC on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products.

  Proposal for a Council Recommendation concerning tests relating to the placing on the market of proprietary medicinal products.

  Proposal for a Council Directive amending Directive 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. [COM(84) 437; 25.9.84]

1985

- Opinion on the :

  Proposal for a Council Directive on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology,

  Proposal for a Council Directive amending Directive 75/318/EEC on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products,

  Proposal for a Council Directive amending Directive 81/852/EEC on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of the testing of veterinary medicinal products

  Proposal for a Council Recommendation concerning tests relating to the placing on the market of proprietary medicinal products

  Proposal for a Council Directive amending 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. [O.J. No. C160, 1.7.85, p18]

1986

- Amendments to the proposals for Council Directives

  on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology.

  amending Directive 75/318/EEC on the approximation of the laws of the Member States relating to analytical , pharmaco-toxicological and clinical standards and protocols in respect of proprietary medicinal products.

  amending Directive 81/852/EEC on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products.

Amendment to the proposal for a Council Recommendation concerning tests relating to the placing on the market of proprietary medicinal products. [COM(86) 117 final; 5.3.86]\

- Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes. [O.J. No. L358, 18.12.86, p1]

- Proposal for a Council Directive relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion within the scope of the national health insurance system. [COM(86) 765; 23.12.86]

1987

- Council Directive 87/18/EEC of 18 December 1986 on the harmonisation of laws, regulations or administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances. [O.J. No. L15, 17.1.87, p29]

- Council Directive 87/19/EEC of 22 December 1986 amending Directive 75/318/EEC on the approximation of the laws of the Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products. [O.J. No. L15, 17.1.87, p31]

- Council Directive 87/21/EEC of 22 December 1986 amending Directive 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. [O.J. No. L15, 17.1.87,p36]

- Council Directive 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high technology medicinal products, particularly those derived from biotechnology. [O.J. No. L15, 17.1.87, p38]

- Council Recommendation of 9 February 1987 concerning tests relating to the placing on the market of proprietary medicinal products. [87/176/EEC; O.J. No. L73, 16.3.87, p1].

- Opinion on the proposal for a Council Directive relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion within the scope of the national health insurance system. [O.J. No. C319, 30.11.87, p47]

1988

- Extension of the pharmaceutical directives to medicinal products not yet covered. [COM(87) 697, 4.1.88]

- Report from the Commission on the activities of the Committee for Proprietary Medicinal Products. [COM(88) 143; 22.3.88]

- Council Directive 88/182/EEC of 22 March 1988 amending Directive 83/189/EEC laying down a procedure for the provision of information in the field of technical standards and regulations. [O.J. No. L81, 26.3.88, p75]

- Amended proposal for a Council Directive relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion within the scope of the national health insurance system. [COM(88) 231; 20.4.88]

- Council Directive 88/320/EEC of 9 June 1988 on the inspection and verification of Good Laboratory Practice (GLP). [O.J. No. L145, 11.6.88, p35]

- Opinion on

  the Commission communication on the extension of the pharmaceutical Directives to medicinal products not yet covered

  the proposal for a Council Directive amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens

  the proposal for a Council Directive extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down additional provisions for medicinal products derived from human blood

- the proposal for a Council Directive extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down additional provisions for radiopharmaceuticals. [O.J. No. C208, 8.8.88, p64]

- Amended proposals for Council Directives

  amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products

  extending the scope of Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens

  extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down additional provisions for medicinal products derived from human plasma

  extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down additional provisions for radiopharmaceuticals. [COM(88) 663, 10.11.88]

1989

- Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion within the scope of national health insurance systems. [O.J. No. L40, 11.2.89, p8]

- Council Directive 89/341/EEC of 3 May 1989 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. [O.J. No. L142, 25.5.89, p11]

The Medicines (Medicines Act 1968)(Amendment) Regulations 1992. [S.I. No. 604]

- Council Directive 89/342/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens. [O.J. No. L142, 25.5.89, p14]

The Medicines (Medicines Act 1968)(Amendment) Regulations 1992. [S.I. No. 604]; The Medicines for Human Use (Marketing Authorizations Etc.) Regulations 1994. [S.I. No. 3144]

- Council Directive 89/343/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for radiopharmaceuticals. [O.J. No. L142, 25.5.89, p16]

The Medicines (Medicines Act 1968)(Amendment) Regulations 1992. [S.I. No. 604]; The Medicines (Application to Radiopharmaceutical - Associated Products) Regulations 1992. [S.I. No. 605]; The Medicines for Human Use (Marketing Authorizations Etc.) Regulations 1994. [S.I. No. 3144]

- Council Directive 89/381/EEC of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down special provisions for medicinal products derived from human blood or human plasma. [[O.J. No. L181, 28.6.89, p44]

The Medicines (Medicines Act 1968)(Amendment) Regulations 1992. [S.I. No. 604]; The Medicines for Human Use (Marketing Authorizations Etc.) Regulations 1994. [S.I. No. 3144]

- Re-examined proposal for a Council Directive extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down additional provisions for medicinal products derived from human blood or human plasma. [COM(89) 178, 26.5.89]

1990

- Commission Directive 90/18/EEC of 18 December 1989 adapting to technical progress the Annex to Council Directive 88/320/EEC on the inspection and verification of good laboratory practice (GLP). [O.J. No. L11, 13.1.90, p37]

- Proposal for a Council Directive on the wholesale distribution of medicinal products for human use.
  Proposal for a Council Directive concerning the legal status for the supply of medicinal products for human use.
  Proposal for a Council Directive on the labelling of medicinal products for human use and on package leaflets. [COM(89) 607; 26.1.90]

- Proposal for a Council Directive widening the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of the laws of the Member States on medicinal products and laying down additional provisions on homeopathic medicinal products.

  Proposal for a Council Directive widening the scope of Directive 81/851/EEC on the approximation of the laws of the Member States on veterinary medicinal products and laying down additional provisions on homeopathic veterinary medicinal products. [COM(90) 72; 22.3.90]

- Proposal for a Council Regulation (EEC) concerning the creation of a supplementary protection certificate for medicinal products. [COM(90) 101; 11.4.90]

- Council Directive 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms. [O.J. No. L117, 8.5.90, p1]

- Proposal for a Council Directive on advertising of medicinal products for human use. [COM(90) 212; 6.6.90]

- Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices. [OJ No. L189, 20.7.90, p17].

The Active Implantable Medical Devices Regulations 1992. [S.I. No. 3146]; The Active Implantable Medical Devices (Amendment and Transitional Provisions) Regulations 1995. [S.I. No. 1671]

- Opinion on the proposal for a Council Directive on the wholesale distribution of medicinal products for human use. [O.J. No. C225, 10.9.90, p18]

- Opinion on the proposal for a Council Directive concerning the legal status for the supply of medicinal products for human use. [O.J. No. C225, 10.9.90, p21]

- Opinion on the proposal for a Council Directive on the labelling of medicinal products for human use and on package leaflets. [O.J. No. C225, 10.9.9.90, p24]

- Future system for the free movement of medicinal products in the European Community.

  Proposal for a Council Regulation (EEC) laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products.

  Proposal for a Council Directive amending Directives 65/65/EEC. 75/318/EEC and 75/319/EEC in respect of medicinal products.

  Proposal for a Council Directive amending Directives 81/851/EEC and 81/852/EEC in respect of veterinary medicinal products.

  Proposal for a Council Directive repealing Directive 87/22/EEC on the approximation of national measures relating to the placing on the market of high technology medicinal products particularly those derived from biotechnology. [COM (90) 283; 14.11.90]

- Opinion on the proposal for a Council Directive widening the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of the laws of the Member States on medicinal products and laying down additional provisions on homeopathic medicinal products. [O.J. No. C332, 31.12.90, p29]

1991

- Report from the Commission to the Council on the activities of the Committee for Proprietary Medicinal Products. [COM(91) 39; 15.2.91]

- Opinion on the proposal for a Council Directive on advertising of medicinal products for human use. [O.J. No. C60, 8.3.91, p40]

- Opinion on the proposal for a Council Regulation (EEC) concerning the creation of a supplementary protection certificate for medicinal products. [O.J. No. C69, 18.3.91, p22]

- Commission Directive 91/356/EEC of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use. [O.J. No. L193, 17.7.91, p30]

- Amendment to the proposal for a Council Directive on the wholesale distribution of medicinal products for human use.

  Amendment to the proposal for a Council Directive on the legal status for the supply of medicinal products for human use.

  Amendment to the proposal for a Council Directive on the labelling of medicinal products for human use and on package leaflets.

  Amendment to the proposal for a Council Directive on advertising of medicinal products for human use. [COM(91) 245; 18.7.91]

- Amendment to the proposal for a Council Directive widening the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of the laws of the Member States on medicinal products and laying down additional provisions on homeopathic medicinal products. [COM(91) 313; 2.8.91]

- Commission Decision 91/448/EEC of 29 July 1991 concerning the guidelines for classification referred to in Article 4 of Directive 90/219/EEC. [O.J. No. L239, 28.8.91, p23]

- Council Directive 91/507/EEC of 19 July 1991 modifying the Annex to Council Directive 75/318/EEC on the approximation of the laws of the Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products. [O.J. No. L270, 26.9.91, p32]

- Opinion on:

  the proposal for a Council Regulation (EEC) laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products,

  the proposal for a Council Directive amending Directives 65/65/EEC, 78/318/EEC and 75/319/EEC in respect of medicinal products,

  the proposal for a Council Directive amending Directives 81/851/EEC and 81/852/EEC in respect of veterinary medicinal products, and

  the proposal for a Council Directive repealing Directive 87/22/EEC on the approximation of national measures relating to the placing on the market of high technology medicinal products particularly those derived from biotechnology. [O.J. No. C269, 14.10.91, p84]

- Future system for the free movement of medicinal products in the European Community.

  Amendment to the proposal for a Council Regulation (EEC) laying down Community provisions for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products.

  Amendment to the proposal for a Council Directive amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products.

  Amendment to the proposal for a Council Directive amending Directives 81/851/EEC and 81/852/EEC. [COM(91) 382; 31.10.91]

1992

- Council Directive 92/25 of 31 March 1992 on the wholesale distribution of medicinal products for human use. [OJ No. L113. 30.4.92, p1]

The Medicines Act 1968 (Amendment) Regulations 1993. S.I. No. 834]

- Council Directive 92/26/EEC of 31 March 1992 concerning the classification for the supply of medicinal products for human use. [OJ No. L113, 30.4.92, p5]

The Medicines (Medicines Act 1968)(Amendment)(No. 2) Regulations 1992. [S.I. No. 3271]; The Medicines for Human Use (Marketing Authorizations Etc.) Regulations 1994. [S.I. No. 3144]

- Council Directive 92/27 of 31 March 1992 on the labelling of medicinal products for human use and on package leaflets. [OJ No. L113, 30.4.92, p8]

The Medicines (Labelling) Amendment Regulations 1992. [S.I. No. 3273]; The Medicines (Leaflets) Amendment Regulations 1992. [S.I. No. 3274]; The Medicines Act 1968 (Amendment)(No. 2) 1994. [S.I. No. 276]; The Medicines for Human Use (Marketing Authorizations Etc.) Regulations 1994. [S.I. No. 3144]

- Council Directive 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use. [OJ No. L113, 30.4.92, p13]

The Medicines (Advertising) Regulations 1994. [S.I. No. 1932]; The Medicines (Monitoring of Advertising) Regulations 1994. [S.I. No. 1933]; The Medicines Act 1968 (Amendment) Regulations 1995. [S.I. No. 2321]

- Council Directive 92/29 of 31 March 1992 on the minimum safety and health requirements for improved medical treatment on board vessels. [O.J. No. L113, 30.4.92, p19]

- Council Regulation (EEC) No. 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products. [O.J. No. L182, 2.7.92, p1]

- Council Directive 92/73/EEC of 22 September 1992 widening the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products and laying down additional provisions on homeopathic medicinal products. [OJ No. L297, 13.10.92, p8]

The Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1994. [S.I. No. 103]; The Medicines (Labelling and Leaflets) Amendment Regulations 1994. [S.I. No. 104]; The Medicines (Homeopathic Medicinal Products for Human Use) Regulations 1994. [S.I. No. 105]; The Medicines (Advertising) Regulations 1994. [S.I. No. 1932]; The Medicines (Monitoring of Advertising) Regulations 1994. [S.I. No. 1933]; The Medicines for Human Use (Marketing Authorizations Etc.) Regulations 1994. [S.I. No. 3144].

1993

- Re-examined proposal for a Council Directive modifying Directives 65/65/EEC, 75/318/EEC and 75/319/EEC relating to medicinal products. [COM(93) 220; 1 June 1993]

- Council Directive 93/42/EEC of 14 June 1993 concerning medical devices. [OJ No. L169, 12.7.93, p1]

The Medical Devices (Consequential Amendments - Medicines) Regulations 1994. [S.I. No. 3119]; The Medical Devices Regulations 1994. [S.I. No. 3017]; The Medical Devices (Consultation Requirements)(Fees) Regulations 1995. [S.I. No. 449]; The Active Implantable Medical Devices (Amendment and Transitional Provisions) Regulations 1995. [S.I. No. 1671]

- Council Regulation (EEC) No. 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products. [OJ No. L214, 24.8.93, p1]

The Medicines for Human Use (Marketing Authorizations Etc.) Regulations 1994. [S.I. No. 3144]

- Council Directive 93/39/EEC of 14 June 1993 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products. [O.J. No. L214, 24.8.93, p22]

- Council Directive 93/41/EEC of 14 June 1993 repealing Directive 87/22/EEC on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology. [O.J. No. L214, 24.8.93, p30]

- Council Directive 93/68/EEC of 22 July 1993 amending Directives 87/404/EEC (simple pressure vessels), 88/378/EEC (safety of toys), 89/106/EEC (construction products), 89/336/EEC (electromagnetic compatibility), 89/392/EEC (machinery), 89/686/EEC (personal protective equipment), 90/384/EEC (non-automatic weighing instruments), 90/385/EEC (active implantable medicinal devices), 90/396/EEC (appliances burning gaseous fuels), 91/263/EEC (telecommunications terminal equipment), 92/42/EEC (new hot water boilers fired with liquid or gaseous fuels) and 73/23/EEC (electrical equipment designed for use within certain voltage limits). [O.J. No. L220, 30.8.93, p1]

1994

- Directive 94/10/EC of the European Parliament and the Council of 23 March 1994 materially amending for the second time Directive 83/189/EEC laying down a procedure for the provision of information in the field of technical standards and regulations. [O.J. No. L100, 19.4.94, p30]

1995

- Council Regulation (EC) No. 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products. [O.J. No. L35, 15.2.95, p1]

- Commission Regulation (EC) No. 540/95 of 10 March 1995 laying down the arrangements for reporting suspected unexpected adverse reactions which are not serious, whether arising in the Community or in a third country, to medicinal products for human or veterinary use authorised in accordance with the provisions of Council Regulation (EEC) No. 2309/93. [O.J. No. L55, 11.3.95, p5]

- Commission Regulation (EC) No. 541/95 of 10 March 1995 concerning the examination of variations to the terms of a marketing authorization granted by a competent authority of a Member State. [OJ No. L55, 11.3.95, p7]

The Medicines (Products for Human Use-Fees] Regulations 1995. [S.I. No. 1116]

- Commission Regulation (EC) No. 542/95 of 10 March 1995 concerning the examination of variations to the terms of a marketing authorisation falling within the scope of Council Regulation (EEC) NO. 2309/93. [O.J. No. L55, 11.3.95, p15]

- Commission Regulation (EC) No. 1662/95 of 7 July 1995 laying down certain detailed arrangements for implementing the Community decision-making procedures in respect of marketing authorizations for products for human or veterinary use. [O.J. No. L158, 8.7.95, p4].

1996

- Opinion of the Economic and Social Committee on the 'Free movement of medicines in the European Union - Abolition of existing barriers'. [O.J. No. C097, 1/4/96, p1].

- Commission Regulation (EC) No. 2141/96 of 7 November 1996 concerning the examination of an application for the transfer of a marketing authorisation for a medicinal product falling iwthin the scope of Council Regulation (EC) No. 2309/93. [O.J. No. L286, 8.11.96, p6].

- Proposal for a European Parliament and Council Directive laying down a procedure for the provision of information in the field of technical standards and regulations. [O.J. C078, 12.3.97, p4.].

Appendix V

European Guidelines Relating to Medicinal Products for Human Use 1983 - 1997

Key to use of the table:

Title of guideline. [Month of adoption; Reference Number; Source of reference]

Abbreviations used:

vol. III	Guidelines on the Quality, Safety and Efficacy of Medicinal Products for Human Use. [Commission of the European Communities (1989b)]
vol. III Addendum	Guidelines on the Quality, Safety and Efficacy of Medicinal Products for Human Use. Addendum. [Commission of the European Communities (1990)]
vol. III Addendum No. 2	Guidelines on the Quality, Safety and Efficacy of Medicinal Products for Human Use. Addendum No. 2. [Commission of the European Communities (1992b)]
vol. III Addendum No. 3	Guidelines on the Quality, Safety and Efficacy of Medicinal Products for Human Use. Addendum No. 3. [Commission of the European Communities (1995)]
III/8290/89	"Status of CPMP guidelines: guidelines published in the series "Rules Governing Medicinal Products in the European Community". [Commission of the European Communities (1994)]
Charlesworth	"Guide to the European Directives concerning Medicines". Charlesworth, F.A., in Griffin (1992).
ICH	International Conference on Harmonisation.
EMEA	*EMEA web site*
n/s	Not specified

Guidelines adopted by the Committee for Proprietary Medicinal Products
1983
Repeated dose toxicity. [October; 83/571/EEC; *vol. III*]
Reproduction studies. [October; 83/571/EEC; *vol. III*]
Carcinogenic potential. [October; 83/571/EEC; *vol. III*]
Pharmacokinetics and metabolic studies in the safety evaluation of new drugs in animals. [October; 83/571/EEC; *vol. III*]
Fixed-combination products. [October; 83/571/EEC; *vol. III*]
1987
Single-dose toxicity. [February; 87/176/EEC; *vol. III*]
Testing of medicinal products for their mutagenic potential. [February; 87/176/EEC; *vol. III*]
Pharmacokinetic studies in man. [February; 87/176/EEC; *vol. III*]
Investigation of bioavailability. [February; 87/176/EEC; *vol. III*]
Clinical testing requirements for drugs for long-term use. [February; 87/176/EEC; *vol. III*]
Clinical investigation of oral contraceptives. [February; 87/176/EEC; *vol. III*]
Clinical investigation of drugs for the treatment of chronic peripheral arterial diseases. [February; 87/176/EEC; *vol. III*]
Non-steroidal anti-inflammatory compounds for the treatment of chronic disorders. [February; 87/176/EEC; *vol. III*]
Anti-epileptic /anticonvulsant drugs. [February; 87/176/EEC; *vol. III*]
Corticosteroids intended for use on the skin. [February; 87/176/EEC; *vol. III*]
Anti-anginal drugs. [February; 87/176/EEC; *vol. III*]
User information on oral contraceptives. [February; 87/176/EEC; *vol. III*]
Data sheets for antimicrobial drugs. [February; 87/176/EEC; *vol. III*]
Chemistry of active ingredients. [February; 87/176/EEC; *vol. III*]
Recommended basis for the conduct of clinical trials of medicinal products in the European Community. [May; n/s; *vol. III*]
Production and quality control of medicinal products derived by recombinant DNA technology. [June; n/s; *vol. III*]
Production and quality control of monoclonal antibodies of murine origin. [June; n/s; *vol. III*]

1988
Development pharmaceutics and process validation. [April; n/s; *vol. III*]
Stability tests on active ingredients and finished products. [July; n/s; *vol. III*]
Pre-clinical biological safety testing of medicinal products derived from biotechnology. [September; n/s; *vol. III*]
Clinical investigation of medicinal products in children. [September; n/s; *vol. III*]
Clinical investigation of medicinal products in the elderly. [September; n/s; *vol. III*]
Antidepressant medicinal products. [September; n/s; *vol. III*]
Quality of herbal remedies. [November; n/s; *vol. III*]
Medicinal products in the treatment of cardiac failure. [November; n/s; *vol. III*]
Antiarrhythmic medicinal products. [November; n/s; *vol. III*]
1989
Analytical validation. [July; n/s; *vol. III Addendum*]
Data sheets for antibacterial medicinal products. [November; n/s; *vol. III Addendum*]
Medicinal products for the treatment of epileptic disorders. [December; n/s; *vol. III Addendum*]
1990
Production and quality control of cytokine products derived by biotechnological processes. [February; n/s; *vol. III Addendum*]
Assessment reports on medicinal products. [February; III/8113/89; *Charlesworth*]
European drug master file procedure for active ingredients. [July; n/s; *vol. III Addendum*]
Production and quality control of human monoclonal antibodies. [July; n/s; *vol. III Addendum*]
Good clinical practice for trials on medicinal products in the European Community. [July; n/s; *vol. III Addendum*]
Clinical testing of prolonged action forms with special reference to extended release forms. [July; n/s; *vol. III Addendum*]
Evaluation of anticancer medicinal products in man. [July; n/s; *vol. III Addendum*]
Pharmacovigilance in the framework of the CPMP. [October; III/8234/89; *III/8290/89*]
Radiopharmaceuticals. [December; n/s; *vol. III Addendum No. 2*]
Recommendations for the development of non-clinical testing strategies. [December; III/58/89; Charlesworth]
Non-clinical local tolerance testing of medicinal products. [December; III/3979/88;*vol. III Addendum No. 2*]

1991
Validation of virus removal and inactivation procedures. [February; III/8115/89; *vol. III Addendum No. 2*]
Radiopharmaceuticals based on monoclonal antibodies. [May; III/3487/89; *vol. III Addendum No. 2*]
Pharmacovigilance exchange of information within the Working Party. [July; III/3366/91; n/s *Charlesworth and III/3567/92*]
Procedure for causality classification in pharmacovigilance in the EC. [July; III/3445/91; *III/8290/89*]
Rapid Alert System. [July; III/3917/90; *III/8290/89*]
Clinical investigation of hypnotic medicinal products. [September; III/3855/89; *vol. III Addendum No. 2*]
Requirements in relation to active substances. [October; n/s; *vol. III Addendum No. 2*]
Harmonization of requirements for influenza vaccine. [October; n/s; *vol. III Addendum No. 2*]
Summary of product characteristics. [October; 9163/90; *Euro Direct*; superseded by III/3567/92]
Definition of a new active substance. [October; III/3036/91; *Euro Direct*]
Dossier check-in procedure. [October; III/3652/91; *III/8290/89*]
Notice to applicants: amendments for radiopharmaceuticals. [October; III/3700/90; *Euro Direct*]
Control authority batch release of poliomyelitis vaccine (oral). [October; III/3516/91; *Charlesworth*]
The use of ionizing radiation in the manufacture of medicinal products. [December; n/s; *vol. III Addendum No. 2*]
Investigation of bioavailability and bioequivalence. [December; III/54/89; *vol. III Addendum No. 2*]
Specifications and control tests on the finished product. [December; III/3324/89; *vol. III Addendum No. 2*]
Medicinal products derived from human blood and plasma. [December; III/8379/89; *vol. III Addendum No. 2*]
Note for guidance on abridged applications. [December; III/3879/90; *III/8290/89*; superseded by III/3567/92]
Minimising the risk of transmission of agents causing spongiform encephalopathies via medicinal products. [December; III/3298/91; *vol. III Addendum No. 2*]
1992
EC application format. [March; III/3038/91; *III/8290/89*; superseded by III/3567/92]
Biotech headings for Notice to Applicants, Part II. [March; III/3153/91; *Euro Direct*]
Operation procedures for the rapporteur and concerned Member States in the multi-state procedure. [March; III/3738/91; *III/8290/89*]

Assessment reports. [May; n/s; *III/3567/92*]

Allergen products. [May; n/s; *vol. III Addendum No. 2*]

Operation procedures for the rapporteur and concerned Member States in the concertation procedure. [May; III/3013/92; *III/8290/89*]

Marketing authorisation application/numbers of copies and languages to be submitted, fee payment schemes.[May; III/3233/92; *III/8290/89*]

CPMP list of allowed terms for the pharmaceutical dosage form, route of administration, container, closure and administration devices. [June; III/3593/91; *Euro Direct*]

SPC for Human normal immunoglobulin i.m. [September; III/3359/92; *III/8290/89*]

SPC for Human immunoglobulin i.v. [September; III/3360/92; *III/8290/89*]

SPC for Human Factor VIII Concentrate. [September; III/3361/92; *III/8290/89*]

SPC for Human Tick-Borne Encephalitis Immunoglobulin i.m. [September; III/3391/92; *III/8290/89*]

SPC for Human Tetanus Immunoglobulin i.m. [September; III/3392/92; *III/8290/89*]

SPC for Human Prothrombin Complex Concentrate. [September; III/3457/92; *III/8290/89*]

SPC for Human Factor IX Concentrate. [September; III/3458/92; *III/8290/89*]

SPC for Antithrombin III. [September; III/3459/92; *III/8290/89*]

SPC for Human Albumin. [September; III/3460/92; *III/8290/89*]

SPC for Anti-D Immunoglobulin, i.m. [September; III/3463/92; *III/8290/89*]

SPC for Anti-Hepatitis B Immunoglobulin i.m. [September; III/3464/92; *III/8290/89*]

SPC for Human Measles Immunoglobulin i.m. [September; III/3467/92; *III/8290/89*]

SPC for Human Rabies Immunoglobulin i.m. [September; III/3468/92; *III/8290/89*]

Quality of prolonged release oral solid dosage forms. [October; III/3172/91; *Vol. III Addendum No. 3*]

SPC for Human Varicella-Zoster Immunoglobulin i.m. [October; III/3479/92; *III/8290/89*]

SPC for Factor VIII Concentrate. [October; III/3526/92; *III/8290/89*]

SPC for Anti Inhibitor Complex Concentrate. [October; III/3527/92; *III/8290/89*

SPC for Human Fibrinogen Concentrate. [October; III/3528/92; *III/8290/89*]

Adaptation of pharmaceutical expert report to radiopharmaceuticals. [October; III/3561/91; *III/8290/89*]

SPC for Human Rubella Immunoglobulin i.m. [October; III/3580/92; *III/8290/89*]

SPC for Human Cytomegalovirus Immunoglobulin i.m. [October; III/3581/92; *III/8290/89*]

Procedure for CPMP guidelines. [October; III/3278/92; *III/8290/89*]

SPC for Human Plasma Coagulation Factor XIII Concentrate. [December; III/3560/92; *III/8290/89*]

Control authority batch release of: adsorbed diphtheria, tetanus, pertussis and combined vaccines; - poliomyelitis vaccine (oral); - monovalent bulk live oral polio vaccine; - measles vaccine; - influenza vaccine. [December; III/3775/92; *Euro Direct*]

Summary of product characteristics (Part 1B) for benzodiazepines used as anxiolytics or hypnotics. [December; III/3653/91; *Euro Direct*]

1993

SPC (Part 1B) of ß-adrenergic blocking agents. [February; 3654/91; *Euro Direct*]

Administrative EC batch release procedure. [February; III/3859/92; *Euro Direct*]

Inventory of computerized systems used by national centres. [March; III/3179/93; *III/8290/89*]

Control authority batch release of: - rubella vaccine; - mumps vaccine; - combined measles, mumps and rubella vaccine. [May; III/3085/93; *Euro Direct*]

European Drug Master File procedure for active ingredients [June; III/5370/93; *Vol. III Addendum No. 3*]

Note for Guidance on the use of the European DMF [Drug Master File] procedure. (Also titled, "Use of the European DMF procedure: A practical guide to implementation by the chemical industry (active ingredient manufacturers) and the pharmaceutical industry (marketing authorisation applicant)"). [June; III/3500/91; *Euro Direct*]

Detection of toxicity to reproduction for medicinal products. [September; III/3387/93; *Vol. III Addendum No. 3*]

Studies in support of special populations - geriatrics. [September; III/3388/93; *Vol. III Addendum No. 3*]

Investigation on chiral active substances. [October; III/3501/91; *Vol. III Addendum No. 3*]

Limitations to the use of ethylene oxide in the manufacture of medicinal products. [December; III/9261/90; *Vol. III Addendum No. 3*]

Stability testing of new active substances and medicinal products. [December; III/3335/92; *Vol. III Addendum No. 3*]

Tc-99m Re-Sulphide (Macro) Colloid. [December; III/3680/92; *III/8290/89*]

Tc-99m MDP. [December; III/3776/92; *III/8290/89*]

Tc-99m HDP. [December; III/3777/92; *III/8290/89*]

Tc-99m DPD. [December; III/3778/92; *III/8290/89*]

Tc-99m Diethyl-IDA (Etifenin). [December; III/3847/92; *III/8290/89*]

Tc-99m Trimethyl-IDA. [December; III/3681/92; *III/8290/89*]

Tc-99m Tin Colloid. [December; III/3846/92; *III/8290/89*]

Tc-99m Trimethyl-Bromo-IDA (Mebrofine). [December; III/3848/92; *III/8290/89*]

Control authority batch release of yellow fever vaccine. [December; III/3084/93; *Euro Direct*]

Se-75 Bile salt (capsules). [December; III/3090/93; *III/8290/89*]

In-111 DTPA (injection). [December; III/3124/93; *III/8290/89*]

Cr-51 EDTA (injection). [December; III/3140/93; *III/8290/89*]

Replacement of chlorofluorocarbons (CFCs) in metered dose inhalation products. [December; III/5378/93; *Vol. III Addendum No. 3*]

Matters relating to the replacement of CFCs in medicinal products. [December; III/5462/93; *Vol. III Addendum No. 3*]

1994

Plastic primary packaging materials. [February; III/9090/90; *Vol. III Addendum No. 3*]

Excipients in the dossier for application for marketing authorisation of a medicinal product. [February; III/3196/91; *Vol. III Addendum No. 3*]

Tc-99m Sulphur Colloid. [III/3679/92; February; *III/8290/89*]

Tc-99m DMSA. [February; III/3120/93; *III/8290/89*]

Tc-99m Gluconate. [February; III/3122/93; *III/8290/89*]

Tc-99m Glucopeptate. [February; III/3123/93; *III/8290/89*]

Tc-99m Albumin Microcolloid millimicrospheres. [February; III/3189/93; *III/8290/89*]

Tc-99m Albumin Microcolloid (um). [February; III/3190/93; *III/8290/89*]

Tc-99m Albumin Nanocolloid (nm). [February; III/3191/93; *III/8290/89*]

I-123 MIBG (injection). [February; III/3246/93; *III/8290/89*]

I-131 MIBG (injection). [February; III/3247/93; *III/8290/89*]

P-32 Na-Phosphate (injection). [February; III/5456/93; *III/8290/89*]

Ga-67 Citrate (injection). [February; III/5458/93; *III/8290/89*]

Tc-99m DTPA. [March; III/3121/93; *III/8290/89*]

Fe-59 citrate (injection). [March; III/5568/93; *III/8290/89*]

Ca-47 chloride (injection). [March; III/5569/93; *III/8290/89*]

Co-57 cyanocobalamin (capsules). [March; III/5573/93; *III/8290/89*]

Cr-51 Na chromate. [March; III/5627/93; *III/8290/89*]

I-123 Na-Iodide (capsules). [May; III/3813/92; *III/8290/89*]

I-123 Na-Iodide (injection). [May; III/3814/92; *III/8290/89*]

Control authority batch release testing of coagulation factors [or clotting factor concentrates]. [May; III/3008/93; *Euro Direct*]

Control authority batch release of albumin. [May; III/3009/93; *Euro Direct*]

Control authority batch release of immunoglobulins. (Also titled, "Control authority batch release of:- human normal immunoglobulin for intramuscular administration; - human normal immunoglobulin for intravenous administration; - human specific immunoglobulins".) [May; III/3010/93; *Euro Direct*]

Tc-99m Albumin. [May; III/3117/93; *III/8290/89*]

Tc-99m MAA. [May; III/3118/93; *III/8290/89*]

Tc-99m Microspheres. [May; III/3119/93; *III/8290/89*]

I-123 Na-Iodide (oral solution). [May; III/3126/93; *III/8290/89*]

Kr-81m Generator. [May; III/3779/92; *III/8290/89*]

Plasma pool testing. [May; III/5193/94; *Vol. III Addendum No. 3*]

Co-58 Cyanocobalamine (solution). [May; III/5574/93; *III/8290/89*]

Combined Co-57 Co-58 Cyanocobalamine. [May; III/5575/93; *III/8290/89*]

In-111 Chloride (injection). [July; III/3380/93; *III/8290/89*]

In-111 Oxinate. [July; III/3381/93; *III/8290/89*]

Control authority batch release of hepatitis B vaccine (rDNA). [July; III/3382/93; *Euro Direct*]

Guideline on adverse reaction reporting by marketing authorisation holders. [September; III/3174/93; *Euro Direct*]

Guideline for marketing authorisation holders on periodic drug safety update reports. [September; III/3175/93; *Euro Direct*]

Draft guideline for marketing authorisation holders on company-sponsored post-marketing safety studies. [September; III/3176/93; *Euro Direct*]

Guideline for marketing authorisation holders on on-going pharmacovigilance evaluation during the post-marketing period. [September; III/3177/93; *Euro Direct*]

Control authority batch release of hepatitis A vaccine. [September; III/5861/93; *Euro Direct*]

Clinical safety data management - definitions and standards for expedited reporting. [November; III/3375/93; *Vol. III Addendum No. 3*]

Dose response information to support product authorisation. [November; III/3376/93; *Vol. III Addendum No. 3*]

SPC of angiotensin converting enzyme inhibitors. [November; III/3816/92; *Vol. III Addendum No. 3*]

The assessment of systemic exposure in toxicity studies. [November; III/5081/94; *Vol. III Addendum No. 3*]

Repeated dose tissue distribution studies. [November; III/5082/94; *Vol. III Addendum No. 3*]

Dose selection for carcinogenicity studies of pharmaceuticals. [November; III/5083/94; *Vol. III Addendum No. 3*]

The extent of population exposure to assess clinical safety for medicines intended for long-term treatment of non-life-threatening conditions. [November; III/5084/94; *Vol. III Addendum No. 3*]
Guideline on the Assessment Report. [November; III/5447/94; *Euro Direct*]
Note for guidance on the presentation of particulars concerning environmental risk assessments for human and veterinary medicinal products which consist of or contain genetically modified organisms. [November; III/5506/94; *Euro Direct*]
Environmental risk assessment for human medicinal products containing or consisting of GMOs. [November; III/5507/94; *Vol. III Addendum No. 3*]
Validation of analytical procedures. [November; III/5626/94; *Vol. III Addendum No. 3*]
I-131 Norcholesterol (injection). [December; III/3142/93; *III/8290/89*]
Tc-99m Generator. [December; III/3143/93; *III/8290/89*]
Production and quality control of medicinal products derived by recombinant DNA technology. [December; III/3477/92; *Vol. III Addendum No. 3*]
Use of transgenic animals in the manufacture of biological medicinal products for human use. [December; III/3612/92; *Vol. III Addendum No. 3*]
Biostatistical methodology in clinical trials in applications for marketing authorisations for medicinal products. [December; III/3630/92; *Vol. III Addendum No. 3*]
Clinical investigation of medical products in the treatment of generalised anxiety disorder, panic disorder and obsessive-compulsive disorder. [December; III/3673/92; *Vol. III Addendum No. 3*]
Control authority batch release of haemophilus type b conjugate vaccine. [December; III/3389/93; *Euro Direct*]
Production and quality control of monoclonal antibodies. [December; III/5271/94; *Vol. III Addendum No. 3*]
Contribution to Part II of the structure of the dossier for applications for marketing authorisation- control of starting materials for blood derivatives. [December; III/5272/94; *Euro Direct*]
Contribution to Part II of the structure of the dossier for applications for marketing authorisation - viral safety studies. [December; III/5512/93; *Euro Direct*]
Revision of the annex 1 to the EU Guide to Good Manufacturing Practice: manufacture of sterile medicinal products (EC). [?; 5808/94; *Euro Direct*]
Gene therapy products: quality aspects in the production of vectors and genetically modified somatic cells. [December; III/5863/93; *Vol. III Addendum No. 3*]
Notice to applicants for marketing authorisations for medicinal products for human use in the European Union (draft). [n/s; III/5944/94; *Euro Direct*]
1995
Note for guidance on the procedure for competent authorities on the undertaking of pharmacovigilance. [June; III/175/95; *EMEA*]
Status of CPMP guidelines: guidelines published in the series "Rules Governing Medicinal Products in the European Community". [n/s; III/8290/89; *Euro Direct*]

Compilation of Community procedures on administrative collaboration and harmonisation of inspections. [n/s; III/5698/94; *Euro Direct*]

Mutual recognition of the SPC. [n/s; III/5880/94; *Euro Direct*]

Intramuscular immunoglobulins: nucleic acid amplification tests for IICV RNA detection. [n/s; III/117/95; *Euro Direct*]

Biological products derived from human urine - viral safety. [n/s;III/118/95; *Euro Direct*]

Genotoxicity: guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals. [September; 141/95, previously numbered III/5225/94; *EMEA*]

Note for guidance on impurities testing: Impurities in new drug substances. [May; III/142/95, previously numbered III/5442/94; *EMEA*]

Guideline for PMS studies for metered dose inhalers with new propellants. [n/s; III/180/95; *Euro Direct*]

Clinical investigation of drugs for the treatment of chronic peripheral arterial occlusive disease. [November; III/233/95, previously numbered III/5936/94; *EMEA*]

Clinical trials on medicinal products in the treatment of cardiac failure. [November; EWP/235/95, previously numbered III/5943/94; *EMEAt*]

Note for guidance on antiarrhythmics. [November; EWP/237/95, previously numbered III/2106/88; *EMEA*]

Clinical requirements for locally applied, locally acting products containing known constituents. [November, EWP/239/95, previously numbered III/3664/92; *EMEA*]

Note for guidance on manufacture of the finished dosage form. [September; III/486/95, previously numbered III/3421/93; *EMEAt*]

Reproductive toxicology: toxicity to male fertility. [December; III/136/95, previously numbered ICH 9; *EMEA*]

Structure and content of clinical study reports. [December; III/137/95, previously numbered ICH 5; *EMEAt*]

Quality of biotechnological products: stability testing of biotechnological/biological products. [December; ICH/138/95, previously numbered III/3772/92 and ICH 7; *EMEAt*]

Quality of biotechnological products: analysis of the expression construct in cell lines used for the production of r-DNA derived protein products. [December; ICH/139/95, previously numbered III/5828/93 and ICH 6; *EMEAt*]

Guideline on the need for carcinogenicity studies of pharmaceuticals. [December; ICH/140/95, previously numbered ICH 8; *EMEAt*]

Procedure for the handling of revisions of opinions issued by the former CPMP. [n/s; MRF 95/1; *Euro Direct*]

1996
Standard operating procedure for scientific advice to be given by the CPMP for innovative medicinal products (EMEA/SOP). [n/s; 002/95; *Euro Direct*]
EMEA Standard Operating Procedure: Centralised Procedure: from assessment reports to European Public Assessment Report (EPAR) (EMEA/SOP). [005/96; *Euro Direct*]
Note for guidance on allergen products. [March; BWP/243/96; *EMEA*]
Guidance on good clinical practice. [July; III/135/95 and ICH 4, previously numbered III/5085/94; *EMEAt*]
Note for guidance to assess efficacy and safety of human plasma derived factor VIII:c and factor IX:c products in clinical trials in haemophiliacs before and after authorisation. [February; III/198/95, previously numbered 5769/94; *EMEA*]
Testing and licensing criteria for fixed combination medicinal products. [April; III/240/95, previously numbered III/5773/94; *EMEA*]
Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses. [February; III/268/95; *EMEA*]
Note for guidance on plasma derived medicinal products. [March; III/269/95; *EMEA*]
Guidelines to assess efficacy and safety of normal intravenous immunoglobulin products for marketing authorisations. [February; III/388/95, previously numbered III/5819/94; *EMEAt*]
Note for guidance on clinical trials with haematopoietic growth factors for the prophylaxis of infection following myelosuppressive or myeloablative therapy. [March; III/555/95; *EMEAt*]
Points to consider in the assessment of anti-HIV medicinal products. [n/s; III/602/95; *Euro Direct*]
Variations: Compilation of documents (EC). [n/s; III/5729/95; *Euro Direct*]
EMEA Standard Operating Procedure: arbitration under the decentralised procedure for marketing authorisation (Article 10, Council Directive 75/319/EEC). [n/s; III/001/96; *Euro Direct*]
Accelerated evaluation of products indicated for serious diseases (life threatening or heavy disabling disease). [n/s; III/495/96; *Euro Direct*]
Notice to applicants for marketing authorisations for medicinal products for human use in the European Union (draft). [n/s; III/5371/96, also numbered III/5429/96; *Euro Direct*]
Note for guidance on evaluation of anti-cancer medicinal products in man. [December; EWP/205/95 *EMEAt*]
Guideline for the photostability testing of new drug substances and products. (ICH) [December; ICH/279/95; *EMEAt*]
Stability testing requirements for new dosage forms (annex). (ICH) [December; ICH/280/95; *EMEA*]
Validation of analytical procedures: methodology. (ICH) [December; ICH/281/95; *Euro Direct*]
Impurities in new drug products (annex). (ICH) [December; ICH/282/95; *Euro Direct*]

Clinical safety data management: periodic safety update reports for marketed drugs. (ICH) [December; ICH/288/95; *EMEA*]

1997

Replacement of animal studies by in vitro models. [February; 728/95; *EMEAt*]

Note for guidance on harmonisation of requirements for influenza vaccine (BWP). [March; BWP/214/96; *EMEAt*]

Note for guidance on clinical investigation of medicinal products in children. [March; EWP/462/95; *EMEAt*]

Note for guidance on core SPC for human immunoglobulin (i.v.) [March; BPWP/859/95; *EMEA*]

Quality of biotechnological products: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin. (ICH) [April; ICH/295/95; *EMEAt*]

Note for guidance on evaluation of new anti-bacterial medicinal products. [April; EWP/558/95 *EMEA*]

Note for guidance on clinical investigation of medicinal products in the treatment of hypertension. [May; EWP/238/95; *Euro Direct*]

Note for guidance on the pharmacodynamic section of the SPC for antibacterial medicinal products. [June; EWP/520/96 *EMEAt*]

Note for Guidance: inclusion of antioxidants and antimicrobial preservatives in medicinal products. [July; QWP; 115/95; *EMEA*]

Note for guidance on genotoxicity: a standard battery testing for genotoxicity testing of pharmacuticals. [September; ICH/174/95; *EMEA*]

Note for guidance on impurities: residual solvents. [September; ICH/283/95; *EMEA*]

Note for guidance on general considerations for clinical trials. [September; ICH/291/96; *EMEA*]

Note for guidance on involutional osteoporosis in women. [September; EWP/552/95; *EMEA*]

Note for guidance on non-clinical safety studies for the conduct of human clinical trials for pharamceuticals. [September; ICH/286/95; *EMEA*]

Note for preclinical safety evaluation of biotechnology-derived products. [September; ICH/302/95; *EMEAt]*

Note for guidance on dose selection for carcinogenicity studies of pharamceuticals: addition of a limited dose and related notes. [September; ICH/366/95; *EMEA*]

Conduct of pharmacovigilance for centrally authorised products. [n/s; 183/97; *Euro Direct*]

Clinical safety data management: data elements for transmission of individual case safety reports (ICH). [September; ICH/287/95; *EMEAt*]

Note for guidance on quality of biotechnological products: derivation and characterisation of cell substrates used for production of biotechnological/biological products (ICH). [September; ICH/294/95; *EMEAt*]

Carcinogenicity: testing for carcinogenicity of pharmaceuticals (ICH). [September; ICH/299/95; *EMEA*]
CPMP position statement on DNA and host cell proteins (HCP), impurities, routine testing versus validation studies. [n/s; BWP/382/97; *Euro Direct*]
Note for guidance on medicinal products in the treatment of Alzheimer's disease. [July; EWP/553/95; *EMEA*]
Year of adoption not specified
Control authority approval of monovalent bulk live oral polio vaccine. [III/3502/91; *Euro Direct*]

Guidelines released for consultation.
Role of the rapporteurs. [III/3479/89; *Charlesworth*]
Role of the Vice-Presidents. [III/8223/89; *Charlesworth*]
Investigation of stereoisomeric active ingredients. [8410/89; *Charlesworth*]
Revision of the Guide to Good Manufacturing Practice: annex on the manufacture of investigational medicinal products (EC). [III/3004/91; *Euro Direct*]
Control authority release of measles vaccine. [III/3193/91; *Charlesworth*]
Control authority batch release of adsorbed diphtheria, tetanus, pertussis and combined vaccines. [III/3454/91; *Charlesworth*]
Antidementia medicinal products. [III/3705/91; *Euro Direct*]
Draft SPC - Tc-99m Sn-MDP (cell labelling). [III/3710/92; *III/8290/89*]
Guideline for competent authorities on the undertaking of pharmacovigilance procedures. [III/3963/92; *Euro Direct*]
Headings for a merged and updated guideline on monoclonal antibodies. [III/3141/93; *Euro Direct*]
Draft SPC - I-125 Fibrinogen (injection). [III/3248/93; *III/8290/89*]
Draft SPC - I-123 Hippurate (injection). [III/3249/93; *III/8290/89*]
Draft SPC - I-125 Hippurate (injection). [III/3250/93; *III/8290/89*]
Draft SPC - Hippurate. [III/3251/93; *III/8290/89*]
Draft SPC - Tc-99m PTP. [III/3252/93; *III/8290/89*]
Draft SPC - Tc-99m Phytate. [III/3253/93; *III/8290/89*]
Draft SPC - Se-75 Norcholestrol. [III/3254/93; *III/8290/89*]
Draft SPC - I-131 Na Iodide (capsules for therapy). [III/3290/93; *III/8290/89*]
Draft SPC - I-131 Na Iodide (capsules for diagnosis). [III/3291/93; *III/8290/89*]
Draft SPC - I-131 Na Iodide (solution). [III/3292/93; *III/8290/89*]
Draft SPC - I-131 Na Iodide (injection). [III/3293/93; *III/8290/89*]
Draft SPC - Xe-133 Xenon (injection). [III/3298/93; *III/8290/89*]
Draft SPC - Xe-133 Xenon (gas). [III/3299/93; *III/8290/89*]
Dossier requirements for type I variations. [III/5783/93; *Euro Direct*]
Variations to a marketing authorisation. [III/5125/94; *Euro Direct*]
Chapters II and III of the "Notice to applicants for marketing authorisations". Mutual recognition and Community referrals. [III/5445/94; *Euro Direct*]

Assessment of potential risks to the environment posed by medicinal products for human use (excluding products containing live genetically modified organisms): Phase I environmental risk assessment. (Also titled, "Phase 1 ecotoxicity assessment of human medicinal products".) [III/5504/94; *Euro Direct*]

Assessment of potential risks to the environment posed by medicinal products for human use (excluding products containing live genetically modified organisms): Phase II ecotoxicity assessment of human and veterinary medicinal products. (Also titled, "Phase II ecotoxicity assessment of human and veterinary medicinal products".) [III/5505/94: *Euro Direct*]

Integration of the evaluation of the environmental risk assessment with the evaluation of the rest of the dossier in support of an application for a marketing authorisation. [III/5508/94; *Euro Direct*]

Validation of virus removal /inactivation procedures: choice of viruses. [III/5543/94; *Euro Direct*]

Validation of virus/removal/inactivation procedures: priority setting. [III/5544/94; *Euro Direct*]

Revision of the Guide to Good Manufacturing Practice: Annex on the manufacture of sterile medicinal products. [III/5808/94; *Euro Direct*]

Clinical investigation of medicinal products in the treatment of hypertension. [III/5931/94; *Euro Direct*]

Clinical investigation of anti-anginal drugs in stable angina pectoris. [III/5946/94; *Euro Direct*]

Data elements for transmission of individual ADR reports. [III/144/95; *Euro Direct*]

Note for guidance on the clinical investigation of anti-anginal medicinal products in stable angina pectoris. [EWP/234/95; *EMEA*]

Note for guidance on plasma derived medicinal products. [BWP/269/95; *EMEA*]

Note for guidance on ethnic factors in the acceptability of foreign clinical data. (ICH) [289/95; *Euro Direct*]

Note for guidance on duration of chronic toxicity testing in animals. [ICH/300/95; *EMEA*]

Note for guidance on pre-clinical pharmacological and toxicological testing of vaccines. [SWP/465/95; *Euro Direct*]

Note for guidance on evaluation of new anti-bacterial medicinal products. [EWP/558/95; *EMEA*]

Note for guidance on the clinical investigation of medicinal products in the treatment of schizophrenia. [EWP/559/95; *Euro Direct*]

Note for guidance on the investigation of drug interactions. [EWP/560/95; *Euro Direct*]

Non-clinical testing of substances with long-term marketing experience (old substances)(SWP). [III/799/95; *Euro Direct*]

Concept paper on a directive on the implementation of Good Clinical Practice and clinical trials (EC Consultative Paper). [III/5608/95; *Euro Direct*]

Start of shelf-life of the finished dosage form (annex to 486/95)(QWP). [III/072/96; *Euro Direct*]

Note for guidance on chemistry of the new active substance. [QWP/130/96; *Euro Direct*]

Note for guidance on development pharmaceutics. [QWP/155/96; *EMEA*]

Reduced stability testing - bracketing and matrixing (annex to 380/95). [157/96; *Euro Direct*]
Maximum shelf-life for sterile products after first opening or following reconstitution (annex to 380/95)(QWP). [III/159/96; *Euro Direct*]
Note for guidance on clinical investigation of drugs used in weight control. [EWP/281/96; *Euro Direct*]
Note for guidance on statistical principles for clinical trials. [363/96; *Euro Direct*]
Note for guidance on specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances. [QWP/367/96; *EMEA*]
Note for guidance on stability testing of existing active substances and related finished products. [QWP/556/96; *Euro Direct*]
Note for guidance on stability testing for a Type II variation to a marketing authorisation. [QWP/576/96; *Euro Direct*]
Annex to ICH/CPMP note for guidance on stability testing of new active substances and medicinal products: declaration of storage conditions for medicinal products in the product particulars. [QWP/609/96; *Euro Direct*]
Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products. [BWP/877/96; *Euro Direct*]
Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. [986/96; *Euro Direct*]
Note for guidance on the pre-clinical evaluation of anticancer medicinal products. [997/96; *Euro Direct*]
Note for guidance on summary of requirements to active substances in part II of the dossier. [QWP/297/97; *Euro Direct*]
Note for guidance on pharmaceutical and biological aspects of combined vaccines. [BWP/477/97; *Euro Direct*]
Concept paper on a Community regulatory framework on Good Manufacturing Practice and certification of starting materials for the industrial manufacture of medicinal products (EC). [EC1; *Euro Direct*]
Guidelines relating to the application of the Council Directive 90/385/EEC on active implantable medical devices and the Council Directive 83/42/EEC on medical devices (EC). [EC2; *Euro Direct*]

Guidelines under discussion
Allergen products. [n/s; *III/8290/89*]
Replacement of animal studies by *in vitro* models. [n/s; *III/8290/89*]
Pre-clinical requirements for trials in gene therapy. [n/s; *III/8290/89*]
Safety pharmacology studies in medicinal producst. [n/s; *III/8290/89*]
Clinical report formatting. [n/s; *III/8290/89*]
Registration requirements for clinical trials with colony stimulating factors. [n/s; *III/8290/89*]
ICH guideline: Characterisation of cell substrates. [n/s; *III/8290/89*]
Quality of water used in non-sterile manufacture. [n/s; *III/8290/89*]
Storage time for multi-doses. [n/s; *III/8290/89*]
Categorisation of medicinal products for use in pregnancy. [III/3862/89; *Euro Direct*]
Stability tests on active ingredients and finished products. (revision) [III/3195/91; *III/8290/89*]
Quality of labelling. [III/3353/91; *III/8290/89*]
Use of preservatives in medicinal products. [III/3713/92; *III/8290/89*]
ICH guideline: Validation of virus inactivation/removal. [III/5834/93; *III/8290/89*]
Assessment report on biotech products. [III/5077/94; *III/8290/89*]
Impurities in new chemical active substances. [III/5110/94; *III/8290/89*]
Procedure for dealing with inspection data. [III/5596/94; *III/8290/89*]
Clinical testing of factors VIII and IX. [III/5769/94; *III/8290/89*]
Clinical testing of immunoglobulins. [III/5819/94; *III/8290/89*]
Draft guideline for competent authorities on the undertaking of pharmacovigilance procedures. [III/5057/95; *III/8290/89*]

Appendix VI

Publications issued by the Medicines Control Agency (1989 - 1997)

Table A *Medicines Act Leaflets which relate to Medicinal Products for Human Use (1972 - 1997).*

MAL 1 (August 1988)	Guide to the Licensing System.
MAL 2 (1989)	Guidance Notes on Applications for Product Licences.
MAL 2 (PI) (April 1987)	Notes on Applications for Product Licences (Parallel Importing).
MAL 4 (1984)	Guidance Notes on Applications for Clinical Trials Certificates and Clinical Trial Exemptions.
MAL 5 (June 1990)	Notes on Applications for a Manufacturer's Licence.
MAL 6 (September 1988)	Notes on Applications for a Wholesale Dealer's Licence.
MAL 8 (December 1995)	A Guide to the Status under the Medicines Act of Borderline Products for Human Use.
MAL 9 (September 1990)	Licensing Provisions affecting Retail Pharmacists.
MAL 13 (August 1990)	Notes on Licensing of Products Sold as "Chemists Own Brands".
MAL 14 (March 1972)	Special Dispensing Services.
MAL 18 (September 1980)	Licensing Requirements involved in the Packaging and Labelling of Medicinal Products.
MAL 21 (November 1982)	Notes on Licensing of Homeopathic Products.
MAL 22 (August 1974)	Application of the Act to Ingredients.
MAL 23 (June 1972)	The Application of Licensing to Non NHS Hospitals.
MAL 24 (June 1990)	Medicinal Products Supply in Course of Giving Advice as to Treatment.
MAL 25 (May 1984).	Notes on Data Sheets.
MAL 29 (September 1992)	Notes on Export Certificates.
MAL 30 (June 1985)	A Guide to the Provisions affecting Doctors and Dentists.
MAL 32 (September 1990)	Clinical Trials using Marketed Products.
MAL 36 (September 1990)	Notes for Guidance on Reproduction Studies.
MAL 37 (September 1990)	The Promotion of Sales of Medicinal Products.
MAL 39 (September 1990)	Products containing Herbal Ingredients.
MAL 41 (May 1982)	Additional Notes for Guidance - Biological Medicinal Products.

Table A contd.

MAL 42 (October 1983)	Notes on the Medicines (Labelling) Regulations 1976.
MAL 44 (July 1977)	Implementation of EEC Directives about the Marketing and Manufacture of Medicinal Products.
MAL 45 (February 1982)	Notes on European Community Requirements about the "Qualified Person".
MAL 46 (September 1990)	Notes on European Community Requirements for the Importation of Proprietary Medicinal Products (for human use).
MAL 47 (August 1983)	Notes on Leaflets supplied with Proprietary Medicinal Products.
MAL 49 (February 1983)	Notes on the Medicines (Labelling) Amendments Regulations 1977.
MAL 55 (April 1978)	Notes on the Medicines (Labelling and Advertising to the Public) Regulations 1978. (SI 1978 No. 41).
MAL 57 (August 1983)	Notes on the Medicines (Advertising to Medical and Dental Practitioners) Regulations 1978.
MAL 58 (June 1987)	Notes on the Preparation of Summaries of Information for Products Subject to the Review Procedure..
MAL 59 (September 1984)	Hearings and Representations under Part II of the Medicines Act 1968.
MAL 60 (June 1979)	Colouring Matters Permitted in Medicinal Products.
MAL 61 (1979)	Notes on Applications for Product Licences and Clinical Trial Certificates. Intra-Uterine Contraceptive Devices.
MAL 77 (April 1997)	Changing the Legal Classification of a Prescription Only Medicine for Human Use.
MAL 80 (October 1993)	New Applications, Regulations and Amendments to Standard Provisions Regulations (Product Licences for Products for Human Use).
MAL 81 (January 1995)	The Medicines for Human Use (Marketing Authorisations etc.) Regulations 1995.
MAL 82 (March 1996)	Changing the legal classification in the United Kingdom of a medicine for human use from pharmacy to general sale list.

Table B MLXs (1990 - 1997).

MLX 179 (29 June 1990)	Proposed amendments to The Medicines (Products other than veterinary drugs)(Prescription Only) Order 1983 (S.I. 1983 No. 1212).
MLX 180 (13 September 1990)	Licence fees for medicinal products for human use only. Proposed amendments to The Medicines (Fees relating to Medicinal Products for Human Use) Regulations 1989 (SI 1989/418, as amended by 1990/210.
MLX 181 (13 September 1990)	Licence fees for medicinal products for human use only. Proposed amendments to The Medicines (Fees relating to Medicinal Products for Human Use) Regulations 1989 (SI 1989/418) in relation to fees for licences and certificates granted under the Medicines Act 1968 and for inspections carried out by Medicines Inspectors.
MLX 182 (18 March 1991)	Proposed amendments to The Medicines (Fees relating to Medicinal Products for Human Use) Regulations 1989 (SI 1989/418, as amended by SI 1990/210 and SI 1990/2326).
MLX 182 (*sic*) (19 September 1991)	Legislative Changes. a. Implementation of European Community Pharmaceutical Directives: 89/341/EEC, 89/342/EEC, 89/343/EEC, 89/381/EEC and 91/356/EEC. b. Fees for applications arising from European Community Extension Directives. c. New abridged licence application procedure. d. Other miscellaneous licensing amendments. e. Minor technical corrections to the fees regulations.
MLX 183	Not issued.
MLX 184 (11 November 1991)	Amendment to Section 28(3)(g) of the Medicines Act 1968.
MLX 185 (25 November 1991)	Proposed amendments to The Medicines (Products for Human Use Fees) Regulations 1991 (SI 1990 No. 1474) and the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (SI 1971 No. 972) as amended.

Table B contd.

MLX 186 (3 January 1992)	Proposed amendments to The Medicines (Products other than Veterinary Drugs)(Prescription Only) Order 1983 (SI 1983 No. 1212).
MLX 187 (6 January 1992)	Proposed Amendments to The Medicines (Products other than Veterinary Products)(Prescription Only) Order 1983 (S.I. No. 1212). Administration of prescription only medicines by ambulance men.
MLX 188 (15 July 1992)	Proposals to amend: Sections 28(3), 86, 91 and 92 of the Medicines Act 1968; the Medicines (Labelling) Regulations SI 1976 No. 1726 as amended; the Medicines (Leaflet) Regulations SI 1977 No. 1055 as amended; the Medicines (Labelling and Advertising to the Public) Regulations SI 1978 No. 41; the Medicines (Advertising to Medical and Dental Practitioners) Regulations SI 1978 No. 1020.
MLX 189 29 July 1992	Implementation of Council Directives concerning the "prescription only" classification for the supply of medicinal products for human and veterinary use: proposed amendments to the Medicines Act 1968.
MLX 190 29 July 1992	Implementation of European Community Directive 91/507/EEC.
MLX 191 15 October 1992	Implementation of European Community Directive 92/28/EEC on the Advertising of Medicinal Products for Human Use.
MLX 192 3 November 1992	Medicines Act 1968: Implementation of the Directive on the Wholesale Distribution of Medicinal Products for Human Use Council Directive 92/25/EEC.
MLX 193	Not issued.
MLX 194 (4 December 1992)	Government Trading Funds Act 1973. Proposed order to enable the Medicines Control Agency to achieve trading fund status.
MLX 195 (5 January 1993)	Proposed amendments to The Medicines (Products other than Veterinary Drugs)(Prescription Only) Order 1983 (S.I. No. 1212).
MLX 196 29 June 1993	Implementation of the European Directive 92/73/EEC on Homeopathic Medicinal Products.
MLX 197 (27 May 1993)	Implementation of the Commission Directive 91/507/EEC (replacing the Annex to 75/318/EEC).
MLX 198 6 July 1993	Proposed amendments to the Medicines (Products other than Veterinary Drugs)(Prescription Only) Order 1983 (SI 1983 No. 1212).
MLX 199 26 August 1993	Implementation of Commission Directive 91/507 (replacing the Annex to 75/318/EEC).
MLX 200 5 October 1993	Implementation of EC Directive 92/28/EEC on the Advertising of Medicinal Products for Human Use.
MLX 201	Proposals to amend The Medicines (Child Safety) Regulations 1975 (as amended). Substitution of British Standard Reference.

Table B contd.

MLX 202 9 December 1993	Proposed amendments to the Medicines (Products for Human Use - Fees) Regulations 1991 (SI 1991 No. 1474) as amended by the Medicines (Products for Human Use - Fees) Amendment Regulations 1992 (SI 1992 No. 756).
MLX 203 10 December 1993	Amendments to the Medicines (Exemption from Licences)(Clinical Trials) Order 1981.
MLX 204 8 December 1993	Medicines Act 1968: Human Medicines: Proposed Amendments to Orders Relating to the Control of Antimicrobial and Biological Substances and Products (SI 1971/1198, SI 1971/1200 and SI 1985/1403).
MLX 205 28 April 1994	Proposed Amendments to: The Medicines (Products other than Veterinary Drugs)(General Sale List) Order 1984 (SI 1984/769); The Medicines (Sale or Supply)(Miscellaneous Provisions) Regulations 1980 (SI 1980/1923); and The Medicines (Pharmacy and General Sale - Exemption) Order 1980 (SI 1980/1924).
MLX 206 6 July 1994	The Medicines for Human Use (Marketing Authorisations, Pharmacovigilance and related Matters) Regulations 1994.
MLX 207 1 July 1994	Proposed Amendments to The Medicines (Products other than Veterinary Drugs)(Prescription Only) Order 1983 (SI 1983/1212).
MLX 208 1 July 1994	Nurse Prescribing Implementation. Proposed Amendments to the Medicines (Products other than Veterinary Drugs)(Prescription Only) Order 1983 (SI 1983/1212).
MLX 209 7 July 1994	Amendments to the Guidance Notes on Applications for Clinical Trials Certificate and Clinical Trial Exemptions.
MLX 210 22 July 1994	Implementation of EC Medical Devices Directive: Implications for Medicines Licensing and for the Committee on Safety of Dental and Surgical Materials.
MLX 211 30 September 1994	Data Sheets/SPCs Amendment of the Regulations.
MLX 212 10 October 1994	Proposed Amendments to the Medicines (Standard Provisions for Licences and Certificates) Regulations.
MLX 213 2 December 1994	Implementation of EC Medical Devices Directive: Drug Device Combination Products - Fees to be Charged to Notified Bodies.
MLX 214 16 December 1994	Medicines Acts 1968, 1971 and Section 21 of the Health and Medicines Act 1988. Licence Fees for Medicinal Products for Human Use Only. Proposals relating to the Making of the Medicines (Products for Human Use-Fees) Regulations 1995 and the Medicines (Homeopathic Medicinal Products for Human Use) Amendment Regulations 1995.
MLX 215 11 January 1995	Proposed amendments to The Medicines (Products other than Veterinary Drugs)(Prescription Only) Order (SI 1983/1212).

Table B contd.

MLX 216 5 May 1995	Proposed Prohibition of the Sale or Supply of Medicinal Products by an Order in accordance with Section 62 of the Medicines Act 1968.
MLX 217 18 May 1995	Proposed Amendments to: The Medicines (Advertising) Regulations 1994 (SI 1994/1932).
MLX 218 11 July 1995	Proposed amendments to: The Medicines (Products other than Veterinary Drugs)(General Sale List) Order 1984 (S.I. 1984/769) and The Medicines (Sale or Supply)(Miscellaneous Provisions) Regulations 1980 (S.I. 1980/1923).
MLX 219 14 July 1995	Proposed amendments to: The Medicines (Products other than Veterinary Drugs)(Prescription Only) Order 1983 (S.I. 1983/1212).
MLX 220	Not issued.
MLX 221 20 November 1995	Licence fees for medicinal products for human use only. Proposals relating to The Medicines (Homeopathic Products for Human Use) Regulations 1994 (as amended in 1995) and The Medical Devices (Consultation Requirements)(Fees) Regulations 1995.
MLX 222 12 January 1996	Proposed Amendments to: The Medicines (Products other than Veterinary Drugs)(Prescription Only) Order 1983 (S.I. 1983/1212).
MLX 223 11 March 1996	Amendment of The Medicines (Advertising) Regulations 1994 [S.I. 1994/1932].
MLX 224	Not issued.
MLX 225 1 August 1996	Proposed Amendments to: The Medicines (Products other than Veterinary Drugs)(Prescription Only) Order 1983 [SI 1983/1212].
MLX 226 20 July 1996	Data Sheet/SPCs Amendment of the Regulations.
MLX 227 21 August 1996	Proposed Amendments to: The Medicines (Products other than Veterinary Drugs)(General Sale List) Order 1984 [SI 1984/769] and The Medicines (Sale or Supply)(Miscellaneous Provisions) Regulations 1980 [SI 1980/1923].
MLX 228 11 November 1996	Administration and Supply of Prescription Only and Pharmacy Medicines by State Registered Chiropodists. Proposed Amendments to The Medicines (Products other than Veterinary Drugs)(Prescription Only) Order 1983 [SI No. 1212] and The Medicines (Pharmacy and General Sale - Exemption) Order 1980 [SI No. 1924]
MLX 229 [8 November 1996]	Proposed Changes to: The UK Adverse Drug Reaction Reporting Scheme - The Yellow Card Scheme.

Table B contd.

MLX 230 [7 November 1996]	Records of Prescription Only Medicines Supplied through Pharmacies. Proposed Amendments to The Medicines (Sale or Supply)(Miscellaneous Provisions) Regulations 1980 [SI No. 1923]
MLX 231 [22 November 1996]	Analgesic Medicines Available without Prescription: Proposed Changes to Product Information and Sale or Supply of Paracetamol.
MLX 232 [3 July 1997]	Proposed Changes to the Supply of Vitamin B6.
MLX 233 [18 December 1996]	Proposed Consolidation of The Medicines (Products other than Veterinary Drugs)(Prescription Only) Order 1983 [SI No. 1212] and Subsequent Amending Orders,
MLX 234 [11 February 1997]	The Prescription Only Medicines Order.
MLX 235 [28 April 1997]	Proposed Amendment to: The Medicines (Products other than Veterinary Drugs)(Prescription Only) Order 1983 (SI 1983/1212) for terfenadine.
MLX 236 [27 March 1997]	Patient Packs: Proposed Amendment to The Medicines (Products other than Veterinary Drugs)(Prescription Only) Order 1983.
MLX 237 [15 April 1997]	Proposed Amendments to: The Medicines (Products other than Veterinary Drugs)(General Sale List) Order 1984 [SI 1984/769] and The Medicines (Sale or Supply)(Miscellaneous Provisions) Regulations 1980 [SI 1980/1923].
MLX 238 24 July 1997	Proposals to Amend The Prescription Only Medicines Order.
MLX 239 21 August 1997	Strengthening of Advertising Controls by the Amendment of Existing Regulations.

Appendix VII

Recipients of MLX Letters

The following "interested organisations" received MLX 206 "The Medicines for Human Use (Marketing Authorisations, Pharmacovigilance and related Matters) Regulations 1994" (6 July 1994):

Advertising Association; Advertising Standards Authority; Association of Community Health Councils of England and Wales; Association of Manufacturers of Medicinal Preparations; Association of Pharmaceutical Importers; Association of the British Pharmaceutical Industry; Asthma and Allergy Research; Biochemical Society; British Association of Homeopathic Manufacturers; British Association of Dermatologists; British Association of Pharmaceutical Physicians; British Association of Pharmaceutical Wholesalers; British College of Optometrists; British Contact Dermatitis Group; British Dental Association; British Dental Association (Northern Ireland); British Dental Association (Scottish Branch); British Dental Association (Welsh Council); British Dental Trade Association; British Herbal Medicines Association; British Homeopathic Association; British Institute of Regulatory Affairs; British Medical Association; British Medical Association (Northern Ireland); British Medical Association (Scottish Branch); British Medical Association; (Welsh Office); British Society for Rheumatology; British Society of Allergy and Clinical Immunology; British Pharmacological Society; Co-operative Union Ltd Parliamentary Committee; College of Health; College of Pharmacy Practice; Company Chemists Association Ltd; Confederation of British Industry; Conference of National Royal Colleges; Consumers Association; Consumers in the European Community Group (UK); Doctor Magazine; English Board for Nursing, Midwifery and Health Visiting; Faculty of Anaesthetists; General Medical Services Committee; General Medical Services Committee (Wales); Guild of Hospital Pharmacists; Health Education Authority; Health Food Manufacturers Association;Independent Healthcare Association; Independent Television Commission; International Research Consultants; Joint Consultants Committee; Medical Defence Union; MIMS Ltd; National Association of Pharmaceutical Distributors; National Consumer Council; National Federation of Consumer Groups; National Institute of Biological Standards and Control; National Pharmaceutical Association; Natural Medicines Group Secretariat; Northern Ireland Consumer Council; Ophthalmic Group Committee; Patients Association; Pharmaceutical Contractors Committee (Northern Ireland); Pharmaceutical General Council (Scotland); Pharmaceutical Services Negotiating Committee; Proprietary Association of Great Britain; Royal College of Anaesthetists; Royal College of General Practitioners; Royal College of Health; Royal College of Midwives; Royal College of Nursing; Royal College of Nursing (Northern Ireland Board); Royal College of Nursing (Wales); Royal College of Obstetrics and Gynaecologists; Royal College of Pathologists; Royal College of Physicians Royal College of Physicians (Edinburgh); Royal College of Physicians and Surgeons (Glasgow); Royal College of Psychiatrists; Royal College of Radiologists; Royal College of Surgeons; Royal College of Surgeons (Edinburgh); Royal College of Surgeons - Faculty of Dental Surgery; Royal College of Surgeons - Faculty of Ophthalmology; Royal

Pharmaceutical Society of Great Britain; Royal Pharmaceutical Society of Great Britain (Scottish Department); Royal Pharmaceutical Society of Great Britain (Welsh Department); Royal Pharmaceutical Society for Northern Ireland; Royal Society of Chemistry; Royal Society of Health; Scottish Biomedical Association; Scottish Consumer Council; Scottish Wholesale Druggists Association; Scrip Ltd; Society of Family Practitioner Committees; Society of Pharmaceutical Medicines; St John Ambulance; Welsh Consumer Council; and Welsh National Board for Nursing, Midwifery and Health Visiting.

Appendix VIII

Publications issued by the Committee on Safety of Medicines

Table A Dear Doctor/Dentist/Pharmacist Letters (1964 - 1997).

DATE	TITLE [SUBJECT MATTER]
4 May 1964	Reporting Adverse Reactions: The Early Warning System.
14 January 1966	Methyldopa and Haemolytic Anaemia.
18 March 1966	Interaction of Monoamine Oxidase Inhibitors and Drugs used in Dentistry.
December 1968	Interaction between Alcohol and Drugs - Telling the Patient.
22 April 1970	Oral Contraceptives Containing Oestrogens
2 August 1972	[Bioinequivalence of Digoxin (Lanoxin)]
4 August 1972	[Bioinequivalence of Digoxin (Lanoxin)]
May 1973	[Clioquinol and SMON; stilboestrol and vaginal adenocarcinoma; interaction of local anaesthetics and antidepressants; anticonvulsants and pregnancy; oestrogen content in oral contraceptives]
3 January 1974	Jaundice following repeated exposure to Halothane.
3 December 1976	Beta-Adrenoceptor-Blocking agents.
7 September 1977	[Lactic Acidosis and Phenformin (Dibotin, Meltrol, Dipar)]
6 October 1977	[Oral Contraceptives and mortality]
23 January 1979	[Establishing of the Committee on Dental and Surgical Materials]
3 August 1982	Opren: Suspension of Product Licences.
1 June 1983	Etomidate (Hypnomidate for Infusion) - PL 0242/0082.
20 June 1983	Etomidate (Hypnomidate Injection and Infusion) PL 0242/0019, 0082
20 October 1983	Use Of Combined Oral Contraceptive Pills and Cancer.
7 March 1984	Phenylbutazone and Oxyphenbutazone.
10 June 1986	Reye's Syndrome and Aspirin Use by Children.
8 October 1986	Desensitising Vaccines (Allergen Extracts) and Anaphylaxis.
12 April 1990	Withdrawal of Pacitron and Optimax.
25 July 1991	Terodiline (Micturin) and Adverse Cardiac Reactions.
1 October 1991	Withdrawal of Triazolam.
18 October 1995	Oral Contraceptives.
21 April 1997	Terfenadine: Proposed Change to Prescription Use.

Table B Adverse Reaction Series Leaflets (1965 - 1985).

DATE	TITLE
No. 1 (February 1965)	Monoamine Oxidase Inhibitors.
No. 2 (August 1965)	Early Warning System.
No. 3 (August 1965)	Some Anti-Arthritic Drugs and a New Analgesic.
No. 4 (January 1967)	Chloramphenicol.
No. 5 (June 1967)	Aerosols in Asthma. Vaccines.
No. 6 (September 1967)	Psychotropic Drugs.
No. 7 (November 1968)	When in Doubt - Report.
No. 8 (May 1969)	Sequential Oral Contraceptives.
No. 9 (December 1969)	Oral Contraceptives containing Oestrogens.
No. 10 (June 1973)	Jaundice and Erythromycin Estolate.
No. 11 (January 1975)	Practolol and Ocular Damage.
No. 12 (February 1975)	Prazosin and Loss of Consciousness.
No. 13 (June 1975)	Hormonal Pregnancy Tests: A Possible Association with Congenital Abnormalities.
No. 14 (May 1977)	Neomycin and Deafness.
No. 15 (July 1977)	Adverse Reactions to Perhexiline Maleate.
No. 16 (November 1977)	Hormonal Pregnancy Tests and Congenital Abnormalities: A Further Statement.
No. 17 (June 1979)	Antibiotic Induced Colitis.
No. 18 (August 1980)	Clofibrate - Mortality in Long Term Use.
No. 19 (January 1985)	Oral Ketoconazole and Liver Damage.

Table C Current Problems (1975 - 1997).

DATE	SUBJECT MATTER
No. 1 September 1975	Beta-adrenergic receptor Blocking Agents; Prazosin; Tetracosactrin; Metoclopramide; Anti-Inflammatory Agents.
No. 2 August 1976	Practolol and other Beta Blockers; Intravenous Anaesthetic Agents; Clindamycin and Lincomycin; Oral Contraceptives; Phenformin; Maprotiline (Ludiomil); Insulin.
No. 3 February 1978	Emepronium Bromide; Methyl Dopa; Metoclopramide; Nitrofurantoin; Drugs and Lactation; Diazepam; Tricyclic Antidepressants; Cotrimoxazole and Benorylate; Althesin.
No. 4 April 1979	Clofibrate (Atromid-S, Liprinal); Nifedipine (Adalat); Practolol (Eraldin); Dextropropoxyphene; Alphaxalone/ Alphadalone (Althesin); Solutions for Intravenous Nutrition; Tardive Dyskinesia; Diflunisal (Dolobid).
No. 5 February 1981	Medicines in Pregnancy; Anticoagulants in Pregnancy; Topical Treatment of Otitis Externa; Benzodiazepines; Thyroxine Tablets BP.
No. 6 July 1981	Sodium Valproate (Epilim); Cimetidine (Tagamet); Cyanocobalamin; Beta Adrenoceptor Antagonists; Timolol Eye Drops (Timoptol); Sodium Cromoglycate; Debendox.
No. 7 December 1981	Mebhydrolin (Fabahistin); Erythromycin; Fluspirilene (Redeptin); Cimetidine; Mianserin (Bolvidon, Norval).
No. 8 October 1982	Piroxicam (Feldene); Amiodarone (Cordarone X); Mianserin (Bolvidon, Norval); Aminocaproic Acid (Epsikapron); Quinidine (Kinidin and Kiditard).
No. 9 January 1983	Sodium Valproate (Epilim).
No. 10 April 1983	Mianserin (Bolvidon, Norval); Ketoconazole (Nizoral); Latamoxef (Moxalactam); Polyethoxylated Castor Oils (Cremophor EL).
No. 11 August 1983	Perhexiline Maleate (Pexid); Zimeldine (Zelmid); Osmosin; Ibuprofen.
No. 12 October 1983	Bupivacaine (Marcain Plain); Isotretinoin (Roaccutane); Fluorescein; Polyethoxylated Castor Oils; Oral Contraceptives.
No. 13 July 1984	Amiodarone (Cordarone X); Ketoconazole (Nizoral); Mucolytics; Maloprim; Bronchodilators; Trazodone (Molipaxin); Macleans Sensitive Teeth Formula Toothpaste; Freefone CSM.

Table C contd

No. 14 February 1985	Hydralazine (Apresoline); Dapsone and Maloprim; Midazolam (Hypnovel); Actifed Syrup; Atracurium Besylate; Dextropropoxyphene; Electronic Reporting of Adverse Reactions.
No. 15 July 1985	Co-trimoxazole, Ampicillin and Trimethoprim; Fansidar; Cyclogest Suppositories and Barrier Contraception; Antidepressants; Dalkon Shield.
No. 16 (No month given) 1986	Non-Steroidal Anti-Inflammatory Drugs; Sodium Fusidate (Fucidin); Amiodarone (Cordarone X); BCG Vaccine; Benorylate (Benoral), Aspirin and Paracetamol; Data Protection Act; Griseofulvin.
No. 17 May 1986	Enalapril (Innovace); Non-Steroidal Anti-Inflammatory Drugs; Dextropropoxyphene; Nifedipine.
No. 18 September 1986	Halothane; Neuroleptic Malignant Syndrome; Yellow Cards or Green Forms?
No. 19 March 1987	Pivmecillinam; Astemizole.
No. 20 August 1987	Non-Steroidal Anti-Inflammatory Drugs; Heminevrin and Alcohol; Beta-Blockers; Etodolac; Propofol; Root Canal Sealants; Accidental Self-Injection of Oil-Based Veterinary Vaccines.
No. 21 January 1988	Benzodiazepines; Spironolactone; Oral Contraceptives; "Red Alert" Scheme.
No. 22 May 1988	Ciprofloxacin and Theophylline; Fluvoxamine (Favarin); Nebuliser Solutions; Opticians' Yellow Card Scheme.
No. 23 September 1988	Vaginal and Rectal Medication; Tetracyclines; Lofepramine (Gamanil); Fenbufen; Viewdata.
No. 24 January 1989	Parentrovite; Fenbufen; Nefopam Hydrochloride (Acupan); Black Triangle Scheme.
No. 25 March 1989	Mianserin (Norval, Bolvidon).
No. 26 May 1989	Oral Contraceptives; Propofol; Fluvoxamine and Fluoxetine; Tamoxifen and Warfarin.
No. 27 December 1989	L-tryptophan; Flecainide (Tambocor); ACE Inhibitors; Misoprostol (Cyotec); Doxycycline; Felbinac (Traxam).
No. 28 May 1990	Chloraseptic; Xamoterol (Corwin); ß2-agonists and Xanthines; ß-blockers; Liquid Paraffin; Heparin.

Table C contd.

No. 29 August 1990	Pimozide; Human Insulins; L-Tryptophan; Propafenone; Glauline (Metipranolol eye drops); Propess controlled release PGE2.
No. 30 December 1990	Vinblastine and Vincristine; Clozaril; Mesalazine (Asacol); Zopiclone (Zimovane); Björk-Shiley heart valves.
No. 31 June 1991	Beta-Agonists; Salmeterol; Fenoterol; Flecainide; Omeprazole; Papaveretum and Noscapine; Björk-Shiley heart valves.
No. 32 October 1991	Terodiline; Carbimazole; Quinolone Antimicrobial Agents; Cephalosporins; Non-Steroidal Anti-Inflammatory Drugs; Sheep Dip Poisoning.
No. 33 February 1992	Beta-Agonists; ACE Inhibitors; ADROIT; Simvastatin.
No. 34 June 1992	Tibolone (Livial); Fenfluramine (Ponderex Pacaps) and Dexfenfluramine (Adifax); Sumatriptan (Imigran); Fluoxetine (Prozac) and Fluvoxamine (Faverin); Propofol (Diprivan).
No. 35 November 1992	Terfenadine; Flucloxacillin; Propofol; Terbinafine (Lamisil); ACE inhibitors; Macrolide antibiotics and Wafarin.
February 1993, volume 19 ("Current Problems in Pharmacovigilance" - new title)	Pharmacovigilance; Paroxetine (Scrotaxt); Co-amoxiclav (Augmentin); Quinolone antibiotics; Misoprostol (Cytotec); Lamotrigine (Lamictal); Reye's syndrome and Aspirin; Drug therapy for tuberculosis.
June 1993, volume 19	Ketorolac (Toradol); sulphasalazine; Was the drug responsible?; reporting reactions to biotechnology reactions; NSAIDs and Aspirin; Non-prescription medicines; Sodium Valproate and Carbamazepine; Fenfluramines.
November 1993, volume 19	Remoxipride (Roxiam); clozapine (Clozaril); drug-induced neutropenia and agranulocytosis; Dysport; thymoxamine (Opilon); Papaveretum injection; medicines newly released for self-medication; leaflets for patients.
February 1994, volume 20	Systemic corticosteroids; L-Tryptophan (Optimax); drug-induced pancreatitis; Dovonex ointment (Calcipotriol); medicines newly released for self-medication; safety assessment of marketed medicines (SAMM); Rifabutin (Mycobutin).
May 1994, volume 20	Desensitising vaccines; antidepressant-induced hyponatraemia; halofantrine (Halfan); neuroleptic sensitivity and dementia; Azapropazone (Rheumox); antibiotic-associated colitis; reporting ADRs to biotechnology products; Thalidomide.
August 1994, volume 20	Oral non-aspirin NSAIDs; Tiaprofenic acid (Surgam); adverse drug reaction reporting; Fluvoxamine.

Table C contd.

November 1994, volume 20	Tamoxifen; high-potency pancreatins; Tibolone (Livial); drug-induced extrapyramidal reactions; Hepatitis A (Havrix).
February 1995, volume 21	Cyproterone acetate (Cyprostat and Androcur); Cisapride (Prepulsid and Alimix); Pimozide (Orap); Tramadol (Zydol); Naftidrofuryl (Praxilene); lipid-lowering drugs; Finasteride (Proscar); CFCs in asthma inhalers; Medicines newly available for self-medication.
July 1995, volume 21	Mesalazine; co-trimoxazole (Septrin, Bactrim, etc.); Tacrolimus (Prograf); Clomiphene (Clomid and Serophene); Ritodrine; Naftidrofuryl infusion (Praxilene Forte); Quinolone antibiotics; views on the yellow card scheme; Thalidomide.
November 1995, volume 21	Measles Rubella vaccine; Paracetamol; Pancreatic enzyme supplements; Summary of Product Characteristics; drugs and driving; medicines newly available for self-medication.
March 1996, volume 22	Cisapride (Prepulsid and Alimix); drug-induced prolongation of the QT interval; Beta-Blockers; Amiodarone (Cordarone X); Vasopressin.
July 1996, volume 22	Alendronate sodium (Fosamax); Mefloquine (Lariam); Ssotalol (Sotacor and Beta-Cardone); Barbiturate hypnotics; Zuclopenthixol (Clopixol and Clopixol Acuphase) and Metolazone (Xuret and Metenix 5); inhaled nitric oxide; Amphotericin; Griseofulvin (Fulcin and Grisovin).
October 1996, volume 22	Hormone Replacement Therapy; Extension of the Yellow Card Scheme to unlicensed herbal remedies; Tramadol (Zydol, Tramake and Zamadol); systemic corticosteroids; Lamotrigine (Lamictal)
February 1997, volume 23	Anorectic agents; drug interactions with grapefruit juice; Ticlopidine; Baclofen; extension of the yellow card scheme to pharmacists; Yellow Card database; Systemic corticosteroids
May 1997, volume 23	Anti-HIV agents; safety issues in anaesthesia; Co-amoxiclav (Augmentin); Lamotrigine (Lamictal)
October 1997, volume 23	Paracetamol and aspirin; Terfenadine; bezodiaepines in pregnancy; Volital (Pemoline); Protease inhibitors; drug-induced birth defects; Methotrexate and blood dyscrasias; ADRS with unlicensed use; Anoretic agents

Table D CSM Updates (1985 - 1988).

DATE	TITLE
5 January 1985	The CSM and Drug Licensing.
2 February 1985	Weighing the Risks.
2 March 1985	Yellow Cards or Blue Screens?
6 April 1985	A Professional Blind Eye?
4 May 1985	Drugs and the Elderly.
1 June 1985	Man Sees What He Suspects.
6 July 1985	Adverse Drug Reactions and the Liver.
7 September 1985	Topical Agents for the Skin: Efficacy and Safety.
5 October 1985	How CSM Data can be used by Doctors.
2 November 1985	Blood Dyscrasias.
7 December 1985	Adverse Reactions to Antidepressants.
4 January 1986	Recurrent Ventricular Tachycardia: Adverse Drug Reactions.
1 February 1986	Cleaning Up the Nation's Medicine Chest.
1 March 1986	Non-Steroidal Anti-Inflammatory Drugs and Serious Gastrointestinal Adverse Reactions - 1.
5 April 1986	Anaesthetists and the Reporting of Adverse Drug Reactions.
3 May 1986	Non-Steroidal Anti-Inflammatory Drugs and Serious Gastrointestinal Adverse Reactions - 2.
14 June 1986	Reye's Syndrome and Aspirin.
5 July 1986	Withdrawal of Nomifensine.
13 September 1986	Annual Review of Yellow Cards - 1985.
11 October 1986	Desensitising Vaccines.
1 November 1986	Anti-Infective Drugs: Adverse Effects reported on Yellow Cards.
6 December 1986	Pregnancy Warnings in Data Sheets.
7 May 1988	Review of Yellow Cards - 1986 and 1987.

Appendix IX

Liability for Defective Products (Directive 85/374).

Article 1 The producer shall be liable for damage caused by a defect in his product.

Article 2 "Product" means all moveables, with the exception of primary agricultural products and game, even though incorporated into another moveable or into an immovable. "Primary agricultural products" means the products of the soil, of stock-farming and of fisheries, excluding products which have undergone initial processing. "Product" includes electricity.

Article 3 "Producer" means the manufacturer of a finished product, the producer of any raw material or the manufacturer of a component part and any person who, by putting his name, trade mark or other distinguishing feature on the product presents himself as its producer.

Without prejudice to the liability of the producer, any person who imports into the Community a product for sale, hire, leasing or any form of distribution in the course of his business shall be deemed to be a producer within the meaning of this Directive and shall be responsible as producer.

Where the producer of the product cannot be identified, each supplier of the product shall be treated as its producer unless he informs the injured person, within a reasonable time, of the identity of the producer or of the person who supplied him with the product. The same shall apply, in the case of an imported product, if this product does not indicate the identity of the importer, even if the name of the producer is indicated.

Article 4 The injured person shall be required to prove the damage, the defect and the causal relationship between defect and damage.

Article 5 Joint and several liability.

Article 6 A product is defective when it does not provide the safety which a person is entitled to expect, taking all circumstances into account, including:

(a) the presentation of the product;

(b) the use to which it could reasonably be expected that the product would be put;

(c) the time when the product was put into circulation.

A product shall not be considered defective for the sole reason that a better product is subsequently put into circulation.

Article 7 The producer shall not be liable as a result of this Directive if he proves:

(a) that he did not put the product into circulation; or

(b) that, having regard to the circumstances, it is probable that the defect which caused the damage did not exist at the time when the product was put into circulation by him or that this defect came into being afterwards; or

(c) that the product was neither manufactured by him for sale or any form of distribution for economic purpose nor manufactured or distributed by him in the course of his business; or

(d) that the defect is due to compliance of the product with mandatory regulations issued by the public authorities; or

(e) 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; or

(f) in the case of a manufacturer of a component, that the defect is attributable to the design of the product in which the component has been fitted or to the instructions of the product.

Article 8 Contributory negligence.

Article 9 "Damage" means:

(a) damage caused by death or by personal injuries;

(b) damage to, or destruction of, any item of property other than the defective product itself, subject to specified limitations.

Article 10 Limitation period of 3 years. The limitation period begins to run from the day on which the plaintiff became aware, or should reasonably have become aware, of the damage, the defect and the identity of the producer.

Article 11 Rights conferred on the injured person are extinguished upon the expiry of a period of 10 years from the date on which the producer put into circulation the actual product which caused the damage, unless the injured person has in the meantime instituted proceedings against the producer.

Article 12 The liability of the producer arising from this Directive may not, in relation to the injured person, be limited or excluded by a provision limiting his liability or exempting him from liability.

Article 13 This Directive shall not affect any rights which an injured person may have according to the rules of the law of contractual or non-contractual liability or a special liability system existing at the moment when this Directive is notified.

Article 14 This Directive shall not apply to injury or damage arising from nuclear accidents and covered by international conventions ratified from the Member States.

Article 15 Each Member State may:

(a) by way of derogation from Article 2, provide in its legislation that within the meaning of Article 1 of this Directive, "product" also means primary agricultural products and game;

(b) by way of derogation from Article 7(e), maintain or, subject to informing the Commission of a proposal, provide in this legislation that the producer shall be liable even if he proves 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 a defect to be discovered.

The operation of the defence in Article 7(e), derogation from that defence and the effect on consumer protection and the functioning of the common market, will be examined 10 years after this Directive comes into force.

Article 16 Producer's total liability for damage may be limited to not less than 70 million ECU.

The effect of this financial limit and its effect on consumer protection and the functioning of the Common Market will be examined 10 years after this Directive comes into force.

Article 17 This Directive shall not apply to products put into circulation before the date on which the provisions come into force.

Article 18	Definition of "ECU"; revision of financial provisions in light of economic and monetary trends in the Community.
Article 19	Member States shall bring into force, not later than three years from the date of notification of this Directive, the laws, regulations and administrative provisions necessary to comply with this Directive.
Article 20	Member States shall communicate to the Commission the texts of the main provisions of national law which they subsequently adopt in the field governed by this Directive.
Article 21	Every five years the Commission shall present a report to the Council on the application of this Directive and, if necessary, shall submit appropriate proposals to it.

Appendix X

Current Position on Implementation of Directive 85/374 in Member States

	Development Risks Defence	*Primary Agricultural Products*	*Financial ceiling*
United Kingdom			
• Consumer Protection Act 1987, Part 1 and Consumer Protection (Northern Ireland) Order 1987.	YES	NO	NO
Entry into force: 1.3.88			
Greece			
• Decree of 31.3.88, published in OJ of 22.4.88	YES	YES	NO
Entry into force 30.7.88.			
[Replaced by Act 2251/94, published in Gazette I, 191 of 16.11.94]			
Italy			
• Decree no. 224 of 24.5.88, published in Gazzetta Ufficiale no. 146 of 23.6.88	YES	NO	NO
Entry into force 29.6.88			
Luxembourg			
• Law of 21.4.89, published in Memorial of 28.4.89	NO	YES	NO
Entry into force 2.5.89			
• Law of 6.12.89, published in Memorial of 27.12.89.			
Denmark			
• Law of 7.6.89, published in Lovtidende A no. 371, p1260	YES	NO	NO
Entry into force 10.6.89			

	Development Risks Defence	*Primary Agricultural Products*	*Financial ceiling*
Portugal			
• Decree no. 383 of 6.11.89, published in Diario da Republica vo. 255, p4880	YES	NO	YES
Entry into force 21.11.89			
Germany			
• Law of 15.12.89, published in Bundesgesetzblatt 1989 I 2198	YES	NO	YES
Entry into force 1.1.90			
* In relation to medicinal products, Germany has a separate scheme.[1]			
Netherlands			
• Law of 13.9.90, published in Staatsblad 1990 no. 487	YES	NO	NO
Entry into force: 1.11.90			
Belgium			
• Law of 25.2.91, published in Belgisch Staatsblaad of 22.3.91 p.5884	YES	NO	NO
Entry into force: 1.4.91			
Ireland			
• Liability for Defective Products Act 1991 (No. 28 of 1991) and S.I. No. 316 of 1991 published by Stationery Office, Dublin 2, PL No. 8520	YES	NO	NO
Entry into force: 16.12.91			

[1]Hodges (1996).

	Development Risks Defence	*Primary Agricultural Products*	*Financial ceiling*
Spain			
• Law No. 22/1994 of 6 July 1994 de responsabilidad civil por los danos causados por productos defectuosos, published in the Boletin Oficial del Estado of 7.7.94, pg 21757	YES*	NO	YES
Entry into force: 8.7.94			
* Except in respect of medicines, food or food products			
Austria			
• Law of 21.1.88, published in Federal Gazette 99	YES	NO	NO
Entry into force: 1.7.88			
[Amended by Law of 11.2.93 and Law No. 510/1994]			
Finland			
• Product Liability Act of 17.8.90, no. 694	NO	YES	NO
Entry into force: 1.9.91			
[Amended by Act No. 99/1993 of 8.1.93 and Act No. 879 of 22.10.93]			
Sweden			
• Product Liability Act of 23.1.92	YES	YES	NO
Entry into force: 1.1.93			
[Amended by Law no. 1137/1992]			

Appendix XI

Outline of The Medicines Act 1968

Appendix XII

Prosecutions relating to Part II of the Medicines Act 1968 (1975 - 1997)

The following is a key to the abbreviations used in this table:

Product Licence [I]:	importation offence
Product Licence [S/S]:	sale or supply offence
Product Licence [M]:	procuring the manufacture
Product Licence [A]:	procuring the assembly
Manufacturer's Licence [M]:	manufacture
Manufacturer's Licence [A]:	assembly

1975		
"A Company" May 1975 [MAIL 8]	Manufacturer's Licence [M/A] (11 charges):	Fine unspecified
1976		
"A Firm" Gravesham Magistrates' Court 4 February 1976 [MAIL 11]	Product Licence [I] (5 charges): Product Licence [S/S] (5 charges): Costs: [A further 14 importation and 14 offences of possession for the purpose of selling were taken into consideration.]	Fined £200 Fined £100 £20
"A Company and a Director" Sheffield Magistrates' Court 25 June 1976 [MAIL 13]	Manufacturer's Licence [M](1 charge): Manufacturer's Licence [A] (1 charge): Product Licence [M] (1 charge): Product Licence [S/S] (1 charge): Product Licence [A](1 charge): Costs:	Company fined £50 Director fined £75 Director fined £40 Company fined £25 Company fined £25 Company fined £25 £25
"A Company" Oldham Magistrates' Court 7 July 1976 [MAIL 14]	Manufacturer's Licence [A] (2 charges): Costs:	Fined £175 £50
"A Company" Manchester Magistrates' Court 14 July 1976 [MAIL 13]	Product Licence [S/S] (5 charges): Costs:	Fined £100 £25
"A Company" Weymouth Magistrates' Court 20 July 1976 [MAIL 13]	Wholesale Dealer's Licence (2 charges): Costs:	Fined £50 £25
"A Company" Liverpool Magistrates' Court 28 July 1976 [MAIL 13]	Product Licence [I] (4 charges): Product Licence [S/S] (4 charges): Costs:	Fined £100 Fined £100 £50
"A Company" Liverpool Magistrates' Court 28 July 1976 [MAIL 14]	Product Licence [I] (3 charges): Costs:	Fined £450 £50
"A Company" Manchester Magistrates' Court 11 August 1976 [MAIL 14]	Product Licence [S/S] (3 charges) Wholesale Dealer's Licence (1 charge) Total Fine: Costs:	 £60 £25
"A Company" Liverpool Magistrates' Court 25 August 1976 [MAIL 14]	Product Licence [I] (5 charges) Product Licence [S/S] (5 charges) Total Fine:	 £100
1977		
"A Company" Bradford Magistrates' Court 8 February 1977 [MAIL 15]	Wholesale Dealer's Licence (1 charge): Costs:	Fined £50 £15

"A Company" Bow Street Magistrates' Court 11 February 1977 [MAIL 15]	Product Licence [S/S] (2 charges): Costs:	3 year conditional discharge £15
"Two Partners in a Firm" Leicester Magistrates' Court 12 March 1977 [MAIL 16]	Product Licence [S/S] (8 charges): Costs:	Fined £800 £20
"A Company" Birmingham Magistrates' Court 24 March 1977 [MAIL 16]	Wholesale Dealer's Licence (5 charges): Costs:	Fined £100 £25
"Two Partners in a Firm" Hendon Magistrates' Court 16 May 1977 [MAIL 16]	Product Licence [I] (? charges) Wholesale Dealer's Licence (? charges) Total Fine (12 charges): Costs:	 £960 £30
"A Firm" Bow Street Magistrates' Court 27 May 1977 [MAIL 17]	Product Licence [I] (4 charges): Costs: [This firm was the subject of a prosecution on 4 February 1976, reported in MAIL 11.]	Fined £400 £30
"A Company" Hornsea Magistrates' Court 15 June 1977 [MAIL 17]	Manufacturer's Licence [A] (3 charges): Costs:	Fined £60 £30
"Two Partners in a Firm" Bolton Magistrates' Court 7 July 1977 [MAIL 17]	Product Licence [I] (? charges) Wholesale Dealer's Licence (? charges) Total Fine (14 charges): Costs:	 £140 £40
"A Company" Clerkenwell Magistrates' Court 30 September & 28 November 1977 [MAIL 19]	Product Licence [I] (? charges): Costs:	Fined £150 £40
"A Company" Bow Street Magistrates' Court 20 October 1977 [MAIL 18]	Product Licence [I] (? charges) Product Licence [S/S] (? charges) Total Fine (17 charges) Costs:	 £1250 £350
"A Company" Birmingham Magistrates' Court 1 November 1977 [MAIL 18]	Product Licence [S/S] (3 charges) Manufacturer's Licence (2 charges) Wholesale Dealer's Licence (6 charges) Total Fine: Costs:	 £230 £30
1978		
"A Company and a Director" Alton Magistrates' Court 23 November 1978 [MAIL 23]	Manufacturer's Licence [A] (1 charge): Costs:	Company fined £150 Director fined £150 £30

1980		
"A Company and a Director" Cleethorpes 3 April 1980 [MAIL 28]	Product Licence [I] (1 charge): Costs:	Company fined £25 Director fined £50 £25
"A Company" Ballymoney 7 July 1980 [MAIL 28]	Wholesale Dealer's Licence (3 charges):	Fined £600
"A Pharmacist" Old Bailey 23 October 1980 [MAIL 29]	Wholesale Dealer's Licence (? charges) Total Fine (? charges): Costs: [*The fine also covered an offence where the pharmacist offered a product not on the General Sales List for retail.]	 £115,000* £7,500
"A Local Businessman" Cheshunt Magistrates' Court 11 November 1980 [MAIL 29]	Manufacturer's Licence [M] (1 charge): Costs:	Fined £200 £75
1981		
"A Company and a Director" Leeds Magistrates' Court 26 March 1981 [MAIL 30]	Wholesale Dealer's Licence (1 charge):	Company fined £50 Director fined £50
"Two Defendants" Newtownards 1 September 1981 [MAIL 33]	Manufacturer's Licence [A] (? charges) Wholesale Dealer's Licence (? charges) Total Fine (3 charges):	 £75 each
1982		
"A Company" Sevenoaks Magistrates Court [MAIL 34]	Product Licence [S/S] (6 charges): Costs:	£1500 £500
"A Person" Billericay Magistrates Court 12 March 1982 [MAIL 34]	Product Licence (5 charges): Costs:	£500 £250
"A Company and a Managing Director" Norwich Magistrates Court 1 July 1982 29 October 1982 (Appeal) [MAIL 36]	Product Licence [I] (? charges) Product Licence [S/S] (? charges) Total Fine (7 charges): Costs (including appeal): [Manager Director pled guilty to four charges and was fined £2,130. There was an appeal and the fine was reduced to £90 for three of the charges, but the fine for the fourth charge was not altered. The revised total of fines is not given. The appeal against sentence by the company was dismissed.]	 £4,230 £750

1983		
"A Person" Bromley Magistrates' Court 24 June 1983 [MAIL 38]	Product Licence [S/S] (2 charges): Costs:	Fined £200 £75
"A Company" Norwich Magistrates' Court 10 November 1983 [MAIL 39]	Product Licence [S/S] (3 charges): Costs:	Fined £2,250 £500
1985		
"A Company" Godstone Magistrates' Court 19 March 1985 [MAIL 43]	Product Licence [I] (7 charges): Costs:	Fined £1,400 £350
"A person" Billericay Magistrates' Court 28 October 1985 [MAIL 46]	Product Licence [S/S] (1 charge) Manufacturer's Licence [A] (1 charge) Total Fine (3 charge): Costs: [*The fine also covered a charge of possession of a misleading leaflet for supply with a medicinal product]	 £300* £50
1986		
"A Company and Two Directors" Dover Magistrates' Court 17 January 1986 [MAIL 47]	Manufacturer's Licence [A] (? charges) Total Fine (? charges): Costs: [*The fine also covered the supply of prescription only medicines without a doctor's prescription and advertising the treatment of specific diseases contrary to the Advertising Regulations.]	 £1,700* £100
"A Defendant" Enniskillen 6 October 1986 [MAIL 49]	Product Licence [I] (? charges) Total Fine (6 charges): Costs: [* The fine also covered possession of illegally imported medicinal products and illegal dealings in prescription only medicines and other medicines not on a general sales list.]	 £1,200* £500
Bharat Kumar Kalyanji Suchak [Farm J, 13 December 1986, p796]	Reprimand [28 October 1986]	
"A Person" Leeds Magistrates' Court 28 October 1986 [MAIL 49]	Product Licence [I] (1 charge): Costs: [A charge of possession of medicinal products for the purposes of wholesale dealing at premises not covered by a wholesale dealer's licence was also taken into consideration.]	£150 £100

1987		
"A Company" Lewes Crown Court 18 March 1987 [MAIL 50]	Product Licence [I] (? charges) Wholesale Dealer's Licence (? charges) Product Licence [S/S] (? charges) Total Fine (7 charges): Costs: [The fine also covers labelling offences.]	 £1,300* £16,300
"A Company" Warwick Magistrates' Court 24 March 1987 [MAIL 50]	Product Licence [I] (? charges) Wholesale Dealer's Licence (? charges) Total Fine (13 charges): Costs: [The fine also covers labelling offences.]	 £850* £500
"A Company" Highgate Magistrates' Court 29 May 1987 [MAIL 51]	Product Licence [S/S] (? charges) Manufacturer's Licence [M] (? charges) Total Fine (10 charges): Costs:	 £5,000 £300
"A Company" Bradford Magistrates' Court 29 June 1987 [MAIL 51]	Product Licence [S/S] (1 charge): Costs:	Fined £500 £500
"A Person" Willesden 8 July 1987 [MAIL 51]	Product Licence [I] Total Fine (5 charges*): Costs: [*Charges also included sale of a prescription only medicine not in accordance with a prescription, advertising and labelling irregularities]	 2 year conditional discharge on each charge. £100
"A Company" Tenbury Wells Magistrate Court 22 July 1987 [MAIL 51] Pharm J, 9 July 1988, p52	Product Licence [I] (6 charges): Costs:	2 year conditional discharge on each charge £50
"A Company" Harrow Magistrates' Court 23 July 1987 [MAIL 51]	Product Licence [I] (? charges): Costs:	1 year conditional discharge £50
"A Company" Bolton Magistrates' Court 7 August 1987 [MAIL 51]	Product Licence [I] (? charges) Total Fine (4 charges): Costs: [*The fine also covered labelling offences.]	 £1,000* £100
Valley Cosmetics Ltd Liskeard Magistrates' Court 8 September 1987 [MAIL 53]	Manufacturer's Licence [M] (1 charge): Product Licence [S/S] (1 charge): Costs:	£50 £50 £50

Waymade Ltd Southend-on-Sea Magistrates' Court 1 October 1987 [MAIL 53]	Product Licence [I] (3 charges): Costs:	£1,000 £20
B.R. Lewis Chemists Ltd Bexleyheath Magistrates' Court 30 October 1987 [MAIL 53] also Pharm J, 8 April 1989, p407	Product Licence [S/S] (? charges) Total Fine (5 charges): Costs: [*The fine also covered labelling offences.]	 £1,400* £100
Herisse Ltd Esher and Walton Magistrates' Court 6 November 1987 [MAIL 53] also Pharm J, 8 July 1989, p50	Product Licence [S/S] (? charges) Wholesale Dealer's Licence (? charges) Total Fine (3 charges): Costs: [*The fine also covered labelling offences.] Pharmacist directors reprimanded [21 March 1989]	 £600* £300
Kalecross Ltd Hendon Magistrates' Court 30 November 1987 [MAIL 53]	Product Licence [I] (? charges) Manufacturer's Licence [A] (? charges) Total fine (4 charges): Costs: [*The fine also covers an advertising offence. The product involved was called "Tabe Treatment".]	 £3,400* £100
Tea Tree Products Dorking Magistrates' Court 7 December 1987 [MAIL 53]	Product Licence [S/S] (1 charge) Wholesale Dealer's Licence (1 charge) Total Fine: Costs: [Product involved was Tea Tree Oil]	 £1,000 £300
1988		
Pharmaceuticals International Wimborne Magistrates' Court 8 January 1988 [MAIL 54]	Product Licence [S/S] (? charges) Manufacturer's Licence [A] (? charges) Total Fine (3 charges): Costs:	 £400 £500
E.W. Guess (Holdings) Ltd Peterborough Magistrates' Court 22 January 1988 [MAIL 54]	Wholesale Dealer's Licence (2 charges) Product Licence [I] (1 charge) Total Fine (4 charges): Costs: [*The fine also covers one labelling offence.]	 £1600* £400
Fetouris International Ltd Uxbridge Magistrates' Court 15 February 1988 [MAIL 54]	Product Licence [I] (2 charges) Costs: [*The fine also covers one advertising offence.]	Fined £1,100* £150
Interport Ltd South Western Magistrates' Court 22 February 1988 [MAIL 53]	Product Licence [S/S] (4 charges): Costs:	£1,650 £300

Whitworth Pharmaceuticals Doncaster Magistrates" Court 29 February 1988 [MAIL 54] also Pharm J, 1 July 1989, p22	Product Licence [S/S] (6 charges): Costs: [*The fine also covers 5 labelling offences.] Pharmacist reprimanded [22 March 1989]	Fined £3,750* £500
Europapharm Ltd and Nationwide Pharmaceuticals Kidderminster Magistrates' Court 10 March 1988 [MAIL 54]	Product Licence [I] (? charges) Total Fine (6 charges): Europapharm: Costs: Nationwide: Costs: [*The fine also covers labelling offences.]	 £2,400* £100 £1,200* £100
Simandon Pharmaceuticals Ltd Leeds Magistrates' Court 17 May 1988 [MAIL 57]	Product Licence [I] (? charges) Total Fine (9 charges): Costs: [*The fine also covers labelling offences.]	 £1,400* £500
Anne Summers (Sales) Ltd [A.S.] and Gold Star Publications Ltd [G.S.] Godstone Magistrates' Court 16 August 1988 [MAIL 57]	Wholesale Dealer's Licence (1 charge): Costs: Product Licence [S/S] (1 charge): Costs:	A.S. fined £500 £300 G.S. fined £750 £300 each
ParadrucoLtd Kidderminster Magistrates' Court 14 December 1988 [MAIL 60]	Product Licence [I] (? charges) Total Fine (3 charges): Costs: [*The fine also covers labelling offences.]	 £3,400* £300
Cory Brothers (Hospital Contracts) Co. Ltd Hendon Magistrates' Court 19 December 1988 [MAIL 58]	Wholesale Dealer's Licence (1 charge): Product Licence [I] (1 charge): Costs:	Fined £1,000 Fined £1,000 £300
Pharmaceuticals International (UK) Ltd and Medispose Ltd trading as Personal Imports (UK) and their Director Wimborne Magistrates' Court 20 December 1988 [MAIL 58]	Product Licence [I] (10 charges): Costs: Pharmacist reprimanded [18 July and 9 August 1989]	£1,500 £500

1989		
Planpharm Ltd Leeds Magistrates' Court 22 May 1989 [MAIL 60]	Wholesale Dealer's Licence (1 charge): Costs:	£100 £200
J. Wademan Doncaster Magistrates' Court 28 September 1989 [MAIL 61]	Product Licence [S/S] (? charges) Wholesale Dealer's Licence (? charges) Manufacturer's Licence [A] (? charges) Total Fine (7 charges): Costs:	 £1,300 £200
Tobyward Ltd Southwark Crown Court 16 November 1989 [MAIL 63]	Product Licence [S/S] (1 charge) Wholesale Dealer's Licence (1 charge) Total Fine: Costs:	 £5,000 £2,000
1990		
Arthur Roy Hampton and Sidney Richard Lister Isleworth Crown Court 16 November 1990 [Pharm J, 25 January 1992, p112]	Three offences Hampton fined £300; Costs £2000 (10 other offences were taken into consideration) Lister fined £750; Costs £2000 (Fine also covered 3 parallel import offences and 21 other offences were taken into consideration] Both reprimanded by the Statutory Committee [19 November 1991]	
Whitecliffe Pharmaceuticals Ltd Chichester Magistrates' Court 28 November 1990 [MAIL 69]	Product Licence [S/S] (? charges) Manufacturer's Licence [M/A](? charges) Total Fine (3 charges): Costs:	 £3,000 £300

1991		
Dr Wells Newark and Southwell Magistrates' Court 4 March 1991 [MAIL 67]	Wholesale Dealer's Licence (1 charge): Costs:	£1,500 £150
Necessity Supplies Ltd Uxbridge Magistrates' Court 25 March 1991 [MAIL 68] Pharm J, 8 May 1993, p638	Wholesale Dealer's Licence (3 charges) Total Fine (7 charges): Costs: [*The fine also covers 4 charges involving labelling offences] Pharmacist director Ketan Himatlal Mehta was reprimanded. [18-19 November 1992]	 £4,000* £500
Transformation (Retail) Ltd Bury Magistrates' Court 28 March 1991 (MAIL 68]	Product Licence [M] (6 charges): Costs:	£1,700 £300
1992		
Mr Yves Delatte Chichester Magistrates' Court 6 January 1992 [MAIL 71]	Product Licence [S/S] (? charges) Manufacturer's Licence [M/A] (? charges) Total Fine (4 charges): Costs: [The charges involved a medicinal product called "Delta Te", which was marketed as a cure for cancer and AIDS.]	 £350 on one charge 2 year conditional discharge for the other 3 charges £150
Mazar Ulrassen Rana Bradford Magistrates' Court 27 January 1992 [MAIL 72]	Product Licence [S/S] (1 charge): Costs: [The product involved contained lead.]	£250 £250
Mohammed Gulami Kanani (Managing Director of Martonland Limited) [Pharm J, 29 August 1992, p261]	No prosecution specified Struck off by the Statutory Committee [30-31 October 1991 and 21-23 July 1992]	

1993		
Mr Murji Shah Isleworth Crown Court 19 February 1993 [MAIL 77]	Product Licence [S/S] (? charges) Wholesale Dealer's Licence (? charges) Total Fine (7 charges): Costs:	 £1,050 £300
Elizabeth Anafo Camberwell Magistrates' Court 13/14 April 1993 [MAIL 77]	Product Licence [S/S] (? charges) Total Fine (? charges): Costs: [*The charges involved unlicensed herbal products and the fine also covered labelling and prescription offences.]	 £750* £250
1994		
Pierre Robert Schaffer Canterbury Crown Court 21 January 1995 [Pharm J, 5 February and 5 March 1994]	Wholesale Dealer's Licence (? charges) Product Licence [I] (? charges) Total Fine (7 charges): Costs: [*The fine also covered labelling and unlawful supply offences. Following on from this case, five pharmacists who dealt with Schaffer have been struck off by the Statutory Committee; more cases are to follow (Pharm J, 2 March p301 and 30 March 1996 p450)]	 £7,000* £5,000
1995		
Derek Adams and Barrie Pye Cardiff Crown Court date not specified [MAIL 90]	Wholesale Dealer's Licence (1 charge): Costs:	Adams fined: £500 not specified
Kevin Haigh (AS Supplies) Bradford Crown Court date not specified [MAIL 90]	Manufacturer's Licence (? charges) Product Licence [S/S] (? charges) Total Fine (? charges) Costs [The charges involved Gamma Hydroxybutyrate (GHB), a "soft designer drug" which has been marketed in other countries; the fine also covered advertising breaches.]	 £1,000 not specified
Tristram Clark Portsmouth Crown Court date not specified [MAIL 90]	Manufacturer's Licence (? charges) Product Licence [S/S] (? charges) Total Fine (? charges) Costs [The charges also involved Gamma Hydroxybutyrate (GHB); the fine also covered advertising breaches.]	 £2,000 not specified
Lillian Maund and Charles Maund Knutsford Crown Court 26 July 1995 [MAIL 91]	(3 charges) Wholesale Dealer's Licence (? charges) Fined Costs: [The charges involved the supply of Sclerovein to trainee beauty therapists]	 £750 each not specified

Robert Hodson Hereford Crown Court 4 September 1995 [MAIL 91]	Product Licence [I] (? charges): Sentenced to 200 hours of Community Service Costs [The charges involved anabolic steroids]	 not specified
John Davies, Martyn Fisher and Justin Huxtable Newport Crown Court 4 September 1995 [MAIL 91]	Product Licence [S/S] (? charges): Costs: Davies was imprisoned for 12 months, suspended to 15 months. [The charges involved Gamma Hydroxy Butyrate (GHB).]	Fined£2,000 not specified
James and Andrew Michaels Luton Crown Court 21 December 1995 [MAIL 93]	Product Licence [M] (1 charge): Costs: [The charge involved Tacrine Hydrochloride (THA); the product was ordered to be destroyed]	12 month conditional discharge £750
Discpharm and Peter Gillespie (Director) Staines Magistrates' Court 1 November 1995 [MAIL 93]	Product Licence [S/S] (1 charge): Costs: Costs: [*The fine also covered a labelling offence. The charges involved Losec.]	Company fined £3,000* £3,000 Director fined £1,500* £1,500
1996		
Shirazali Panjawani Wood Green Crown Court 22-25 January 1996 [MAIL 94]	Wholesale Dealer's Licence (3 charges): Costs:	£4,500 £1,000
1997		
Mapleleaf Holdings Ltd Manchester Crown Court 17 March 1997 [MAIL 101]	Manufacturer's Licence 2 offences: Costs: [Involved the marketing of "Double Strength Oestrogen Hormone Breast Cream", Anti-Androgen Hormone Body Hair Retardant", "Oestrogen Breast Development Cream" and "Hormone Beard Retardant" to transsexuals. Other charges advertising contrary to section 95 of the Medicines Act, sale of products not on the general sale list and sale of prescription only medicinal products. Total fine was £6,750]	 £1500 £15038

Appendix XIII

"Highlights and Achievements" of the Medicines Control Agency (1990 - 1997)

These "highlights and achievements" are set out in the Annual Reports of the Medicines Control Agency

1990/91

- *average time to New Drugs Assessment - 74 working days*
- *UK Rapporteur to more than 30 per cent of work through EC biotechnology and high technology procedures*
- *per cent of multi-state applications arose from the UK*
- *Abridged Licensing backlog reduced by 30 per cent*
- *PL/PI licensing backlog reduced by 60 per cent*
- *Review of medicines completed*
- *ADROIT implemented*
- *ADR reports computerised and screened*
- *inspections undertaken*
- *samples tested*
- *per cent of export certificates granted within 48 hours*
- *Addendum 1990 to the British Pharmacopoeia published*
- *appeals considered by the Medicines Commission*

1991/1992

- *ADROIT fully operational*
- *Average time for NCE assessment: 115 working days*
- *Time to assessment for abridged applications: cut by 66 per cent*
- *Abridged licensing backlogs eliminated*
- *UK main rapporteur for applications received under EC procedures*
- *Successful negotiation of seven EC directives*
- *Stable financial and fees structure established*
- *Government Executive Agency status achieved*

1992/1993

- *Efficiency improved without loss of quality or effectiveness*
- *Important new medicines authorized for patients earlier*
- *Almost all high level targets met and licensing backlogs eliminated*
- *Successful introduction of simplified licensing procedure for change in product licence ownership*

1992/1993 contd.

- *Large intakes of applications for abridged, variations, renewals and parallel imports successfully processed*
- *Acted as the rapporteur for 37% of European Community multistate and 44% of EC concertation procedures*
- *edition of the British Pharmacopoeia completed*
- *Electronic pharmacovigilance networks introduced between MCA and industry and MCA and some EC member states*
- *Demanding inspection targets met and major improvements in service for export licences*
- *Major progress on IT initiatives PLUS, CTX and BLIS database*
- *New procedures to improve performance on "Prescription Only Medicines" to "Pharmacy" switch (POM to P)*
- *Played a lead role in implementing EC directives*
- *Successfully negotiated EC homeopathic directive on behalf of UK adopted in September 1992*
- *Financially self-sufficient and achievement of Trading Fund status*
- *No increase in fees 1993/94.*

1993/94[1]

- *Agreement reached on important new guidelines on the Safety Assessment of Marketed Medicines (SAMM)*
- *Completion of negotiations and implementation of the Future Systems legislation and the Homeopathic Directive*
- *Involved in negotiating and implementing EC Directives on packaging, general product safety, distance-selling and the notification of technical requirements*
- *ISO 9002 achieved by the Inspection Unit*
- *Three new publications "Towards Safe Medicines", "Working with Business" and "Rules and Guidance for Pharmaceutical Manufacturers"*
- *Operated successfully as a trading fund*

1994/95

- *Operated successfully as a Trading Fund*
- *UK regulations implemented on target to create new licensing system, bringing UK law in line with EC legislation*
- *World leader in POM to P switches and introduction of twin track procedure*
- *Further steps taken on deregulation, 75 regulations reviewed, 21 deregulated*

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[1]The MCA did not summarise its "highlights" for this year! However, the Author has suggested a few possibilities.

1994/95 contd.

- *Record number of samples tested under the Medicines Testing Scheme, exceeding target*
- *Improved enforcement with MCA investigative officers trained to police standards*
- *Production of a public information leaflet, explaining in simple terms medicines control in the UK*
- *New complaints procedure introduced in line with Open Government and Citizen's Charter initiatives*
- *Continued priority for pharmacovigilance and public health protection*
- *Working toward accreditation award in "Investors in People"*
- *Introduction of new training initiatives particularly concentrating on European issues*
- *Staff refreshment facilities enhanced*
- *Sports and social club set up*
- *Fastest assessing authority for new active substances at 56 days*
- *Fastest export certification scheme in the world, a great support for UK exporters*
- *Fees level held for third year and for 1995/96 to be overall 4% lower*
- *Introduction of electronic reporting for companies to facilitate adverse drug reactions reporting*
- *Assessment and queuing times for committee appeals reduced to the shortest ever recorded*
- *Played leading role in development of the new European licensing system, including production of a guide to the Future System and continued EuroDirect subscription service*
- *Issued first homeopathic registration licence in EC*
- *Implemented EC Directive on Medicines Advertising*
- *Acceptance of our medical terminology MEDDRA, as the basis for the future medical terminology for international drug regulatory affairs*

1995/96

- *Played leading role in pharmacovigilance and public health within EU.*
- *Fastest assessing authority for both new active substances and abridged applications.*
- *Leading Reference Member State in the European Mutual Recognition system.*
- *First Member State to introduce the new EU system for variations of marketing authorisations.*
- *European leader for overseas inspections carried out at the request of the EMEA.*
- *Product Licensing database (PLUS) launched providing better service for industry.*
- *World leader in reclassification - ten further POM to P switches.*
- *Three major changes to general sales list (GSL) Order.*
- *Patient Pack Initiative launched.*
- *Record number of samples tested under the Medicines Testing Scheme, at lower unit cost.*
- *Central Enquiry Point handled 7,000 enquiries and provided specialist briefing on key issues.*

1995/96 contd.

- *Two new videos produced on UK drug regulation system in action.*
- *Operated successfully as a Trading Fund.*
- *Fees reduced for third year running, overall 4% last year, and overall 2% for 1996/97.*
- *Further steps taken on deregulation, particularly clinical trials and replacement of data sheets with SPCs.*
- *Published revised clinical trial guidelines.*
- *Action plan put in place for "Investors in People" accreditation.*
- *Continuing education programme for each professional staff group.*
- *New IT training programme launched.*

1996/97

- *Effectively promoted high standards of public health through the process of medicines control.*
- *Served Ministers, the UK Licensing Authority and contributed substantially to European Community procedures in medicines control.*
- *Effectively managed the resources of the Agency, achieved significant efficiency gains and reduced fees for the fourth consecutive year,*
- *Provided value for money and improved standards of service to the pharmaceutical industry.*
- *Achieved almost all of its high level targets.*
- *Achieved Highly Commended in the annual Charter Mark awards.*
- *Jointly hosted the third European Conference of Medicines Agencies.*
- *All high levels targets have been met in the assessment of new drug applications: 39 assessed in a mean time of 43 days.*
- *MCA established as a leading player in both the European Centralised and Mutual Recognition procedures.*
- *1,147 applications determined.*
- *98 per cent of all abridged applications assessed within 100 days.*
- *Clinical trial high level targets achieved with applications received from 40 new companies.*
- *Record number of 570 parallel import applications determined.*
- *Start of Remote Access to Marketing Authorisation (RAMA) project to allow remote access to the Agency's licensing database. This will increase the supply of information to licence holders and allow the receipt of electronic dossiers.*
- *1997 Addenda to British Pharmacopoeia published in December 1996.*
- *Leading European role in pharmacovigilance within the EU.*
- *Use of three UK record linkage databases for rapid investigation of possible drug safety hazards.*
- *Handled record number of 15,000 variations to marketing authorisations, stringent target times met.*

1996/97 contd.

- *Highest number of variations handled as EU Reference Member State in the Mutual Recognition procedure.*
- *Record number of reclassifications assessed, 24 POM to P switches, 35 P to GSL.*
- *Completed comprehensive inspection audits to confirm the safety of UK pharmaceuticals with respect to guidelines on the use of bovine derived materials in medicines.*
- *Introduced Inspectorate for Good Clinical Practice (GCP).*
- *Played leading role in conducting overseas inspections for the European Community.*
- *Successful major initiatives against the counterfeiting of medicines.*
- *Seven further deregulatory measures introduced.*
- *Updated and enlarged the MCA's website, incorporating the CSM sub-site.*
- *Introduction and expansion of compact disk services across the Agency.*
- *Encouraged a record number of staff to enrol for professional qualifications.*
- *Launched new senior management training programme.*
- *Further improved and extended the distribution of EuroDirect publications.*

Appendix XIV

Members of the Medicines Commission, CSM, together with its Sub-Committees and External Advisers, British Pharmacopoeia Commission, Management Board of EMEA, CPMP and ABRHP (1997)

Members of the Medicines Commission (1997).[1]

Professor D.H. Lawson (Chairman)	Consultant Physician, Glasgow Royal Infirmary, Honorary Professor of Medicine, University of Glasgow, Visiting Professor, University of Strathclyde.
Dr R. Auty	Development Director, Zeneca Pharmaceuticals.
Professor S. Campbell	Professor of Obstetrics and Gynaecology and Head of Department, St George's Hospital Medical School, Tooting, London.
Professor S. Davis	Lord Trent Professor of Pharmacy and Head of Department, Nottingham University.
Professor A. Dayan	Professor of Toxicology, St Bartholomew's Hospital, London.
Professor E. Ernst	Director of the Department of Complementary Medicine, University of Exeter.
Professor R. Jones	Professor of Veterinary Anaesthesia, Royal Liverpool University Hospital
Dr P. Kumar	Reader in Gastroenterology and Hon. Consultant Physician at the Royal Hospitals Trust - St Bartholomew's and the Royal London Hospitals and Homerton Hospital Trust.
Miss A. Lewis	Joint Director, Centre for Pharmacy Postgraduate Education, University of Manchester,
Dr C. McCartney	Assistant Director of the Central Public Health Laboratory, London
Dr A. McKnight	Regional Director of Postgraduate General Practice Education, Northern Ireland.
Mr D. Miller	Adviser on Medicines to British Veterinary Association.
Dr C. Newdick	Reader in Health Law, University of Reading.
Professor J.M. Newton	Head of Department of Pharmaceutics, The School of Pharmacy, University of London.
Professor S. Pocock	Professor of Medical Statistics, London School of Hygiene & Tropical Medicine.
Dr A. Renwick	Reader in Clinical Pharmacology, University of Southampton.
Mrs J. Shott	Associate Director, Procter & Gamble.
Professor P.S.J. Spencer	Professor of Pharmacology and Head of School, Welsh School of Pharmacy, University of Wales.
Dr D. Williams	Director, Anitox Ltd.
Mr C. Wilson	General Veterinary Practitioner, Fife.

[1]Medicines Commission et al (1997) p8.

Members of the Committee on Safety of Medicines (1997)[2]

Professor M.D. Rawlins (Chairman)	Professor of Clinical Pharmacology, University of Newcastle upon Tyne.
Professor A.M. Breckenridge (Vice-Chairman)	Professor of Clinical Pharmacology, University of Liverpool.
Professor T.R.E. Barnes	Professor of Clinical Psychiatry, London University.
Dr K.L. Costeloe	Head of Department of Child Health and Reader in Neonatal Medicine, St Bartholomew's & the Royal London School of Medicine & Dentistry.
Dr J.H. Darbyshire	Head of the MRC's HIV Clinical Trials Centre, University College, London Medical School.
Professor H.J. Dargie	Consultant Cardiologist and Co-Director of CRI in Heart Failure, Glasgow University.
Professor D.S. Davies	Professor of Biochemical Pharmacology, Royal Postgraduate Medical School, Hammersmith Hospital, London.
Dr A.M. Douglas	General Practitioner, Exeter.
Professor G.W. Duff	Professor of Molecular Medicine, Sheffield University.
Dr S.Y. Eykyn	Reader in Clinical Microbiology, St Thomas' Hospital, London.
Professor R.G. Finch	Professor of Infectious Diseases, Nottingham University.
Professor A.T. Florence	Dean of the School of Pharmacy, London University.
Professor E.C. Gordon-Smith	Professor of Haematology, St George's Hospital Medical School, London.
Professor K. Gull	Director of the Research and Graduate School, School of Biological Sciences, Manchester University.
Professor H.S. Jacobs	Professor of Reproductive Endocrinology, University College and Middlesex School of Medicine, London.
Mrs E.A. Kay	Director of Clinical Pharmacy, United Leeds Teaching Hospital Trust.
Dr M.J. Kendall	Reader in Medicine, Birmingham University.
Dr B.J. Kirby	Consultant Physician and Deputy Director, Postgraduate Medical School, Exeter University.
Dr S. Kumar	General Practitioner, Widnes, Cheshire.
Professor M.J.S. Langman	Professor of Medicine and Dean of the Faculty of Medicine and Dentistry, Birmingham University.
Dr. A.V.P. MacKay	Medical Director of the Argyll and Bute NHS Trust and McIntosh Lecturer in Psychological Medicine, Glasgow University.
Professor J.M. Midgley	Professor of Pharmaceutical and Medicinal Chemistry, Strathclyde University.
Professor B.K. Park	Professor of Pharmacology and Therapeutics, Liverpool University.
Professor B.L. Pentecost	Consultant Physician and Director of British Heart Foundation.

[2]Medicines Commission et al (1997) p24.

Members of the Committee on Safety of Medicines contd.

Professor J.C. Petrie	Professor of Clinical Pharmacology, Aberdeen University.
Professor L.L. Smith	Director of the MRC Toxicology Unit, Leicester University.
Professor R.L. Souhami	Professor of Clinical Oncology, University College London Medical School.
Dr K. Verrier Jones	Senior Lecturer in Paediatric Nephrology, Cardiff Royal Infirmary.
Professor M.P. Vessey	Professor of Public Health, Oxford University.
Professor I.V.D.. Weller	Head of Department of Sexually Transmitted Disease, University College London Medical School.

Sub-Committee on Biologicals (1997)[3]

Professor H.S. Jacobs (Chairman)	Professor of Reproductive Endocrinology, University College and Middlesex School of Medicine. Also CSM member.
Professor K. Gull (Vice-Chairman)	Director of the Research and Graduate School, School of Biological Sciences, Manchester University. Also CSM member.
Dr D.H. Calam	Head of Chemistry and Antibiotics, National Institute for Biological Standards and Control. Also CPS and BPC member.
Professor G.W. Duff	Professor of Molecular Medicine, Sheffield University. Also CSM member.
Professor F.G.H. Hill	Consultant Haematologist, Birmingham Children's Hospital.
Professor J. Melling	Director, Salk Institute for Biological Studies, Swiftwater, USA
Dr G.C. Schild	Director of the National Institute for Biological Standards and Control.
Professor The Hon R.S. Tedder	Head of Virology, University College and Middlesex School of Medicine.
Dr R. Thorpe	Head of Immunobiology, National Institute for Biological Standards and Control.
Professor J.M. Walker	Professor and Head of Biochemistry, Hertfordshire University.

[3]Medicines Commission et al (1997) p30

Sub-Committee on Chemistry , Pharmacy and Standards (1997)[4]

Professor A.T. Florence (Chairman)	Dean of the School of Pharmacy, London University. Also CSM member.
Professor J.M. Midgley (Vice-Chairman)	Professor of Pharmaceutical and Medicinal Chemistry, Strathclyde University. Also CSM and BPC member
Dr D.H. Calam	Head of Chemistry and Antibiotics, National Institute for Biological Standards and Control. Also Biologicals and BPC member
Dr A.G. Davidson	Head of Medicines Testing Laboratory, Edinburgh
Professor D. Ganderton	Chairman, British Pharmacopoeia Commission.
Professor C. Marriott	Professor of Pharmaceutics, King's College, London.
Dr R.J. Pinney	Head of Microbiology, School of Pharmacy, London University.
Professor A. Li Wan Po	Professor of Pharmaceutics, Nottingham University.
Professor G.T. Tucker	Professor of Clinical Pharmacology, Sheffield University.

Sub-Committee on Pharmacovigilance (1997)[5]

Professor A.M. Breckenridge (Chairman)	Professor of Clinical Pharmacology, Liverpool University. Also CSM member.
Dr J.H. Darbyshire (Vice-Chairman)	Head of the MRC's HIV Clinical Trials Centre, University College Medical School. Also CSM member.
Dr K. Beard	Consultant Physician in Geriatric Medicine, The Victoria Infirmary, Glasgow.
Mrs Anne Lee	Principal Pharmacist, Area Drug Information Centre, Glasgow, Royal Infirmary.
Dr T.M. MacDonald	Senior Lecturer and Hon. Consultant Physician, Department of Clinical Pharmacology, Dundee University.
Professor K. MacPherson	Professor of Public Health Epidemiology, Health Promotion Unit, London School of Hygiene and Tropical Medicine.
Dr M. Pirmohamed	Lecturer in Clinical Pharmacology and Therapeutics, Liverpool University.
Professor L.E. Ramsay	Consultant Physician at Hallamshire Hospital and Reader in Clinical Pharmacology and Therapeutics, Sheffield University. Also BPC member.

[4]Ibid p32.
[5]Ibid p33.

External Advisory Panel to the Medicines Control Agency and the Committee on Safety of Medicines (1997)[6]

Mrs Dorothy A. Anderson	Director, Dental Practice Division (Common Service Agency), Edinburgh.
Miss Mary M. Anderson	Consultant Obstetrician and Gynaecologist, Lewisham Hospital.
Dr Deborah Ashby	Reader in Medical Statistics, Liverpool University.
Professor L.R.I. Baker	Consultant Physician and Nephrologist, The Royal Hospital of St Bartholomew, London.
Professor R.W. Baldwin	Professor of Tumour Biology, Nottingham University.
Dr D.N. Bateman	Consultant Physician and Reader in Therapeutics Freeman Hospital, Newcastle and Newcastle University and Director of Northern and Yorkshire Regional Drug and Therapeutics Centre.
Professor Sir Colin L. Berry	Professor of Morbid Anatomy, St Bartholomew's & Royal London School of Medicines and Dentistry.
Dr J.B. Bingham	Consultant Radiologist, Guy's Hospital.
Professor W. Bonfield	Director, Interdisciplinary Research Centre in Biomedical Materials, Queen Mary's and Westfield College, University of London.
Professor J.R. Brown	Professor of Pharmaceutical and Medicinal Chemistry and Deputy Chief Executive/Pro Vice-Chancellor, Sunderland University.
Professor C. Bucke	Professor of Biotechnology, Westminster University.
Mr R.J. Buckley	Consultant Ophthalmologist and Director, Contact Lens Department, Moorfield Eye Hospital, London.
Dr Jill A. Bullimore	Consultant Oncologist, Bristol Oncology Centre, Bristol.
Dr R.T. Calvert	Director of Pharmacy and Sterile Service Department, Leeds General Infirmary.
Professor R.D.R. Camp	Professor of Dermatology, and Director, Graduate School of Biological Sciences and Medicine, University of Leicester.
Dr E. Mary Cooke	Deputy Director, Public Health Laboratory Service Board, London.
Dr Griselda M. Cooper	Senior Lecturer in Anaesthesia, Birmingham University & Regional Adviser West Midlands.

[6]Ibid pp34 - 39. The Annual Report also specifies which members of the External Advisory Panel have attended meetings and/or provided written advice to the various committees.

External Advisory Panel contd.

Professor D.J.G. Davies	Head of the School of Pharmacy and Pharmacology, Bath University.
Professor Kay E. Davies	Professor of Genetics, Genetics Laboratories, Department of Biochemistry, Oxford University.
Dr M.J. Denham	Consultant Geriatrician, Northwick Park Hospital, London.
Dr G.M. Eccelston	Senior Lecturer in Pharmaceutics, Strathclyde University.
Professor H.D. Edmondson	Professor of Oral Surgery and Medicine, Faculty of Medicine and Dentistry, Birmingham University.
Dr E. Elias	Consultant Physician, Queen Elizabeth Hospital Medical Centre, Birmingham.
Dr P.B. Farmer	Senior Scientist, MRC Toxicology Unit, Leicester University.
Professor J.P.H. Fee	Professor of Anaesthesia, Queen's University, Belfast.
Dr R.E. Ferner	Consultant Physician, Birmingham Hospital & Clinical Toxicologist West Midlands Poisons Unit and Senior Lecturer in Clinical Pharmacology, Birmingham University.
Dr Anne F. Glasier	Consultant Gynaecologist and Director, Family Planning and Well Women Services, Edinburgh Healthcare, NHS Trust.
Dr Elizabeth Graham	Consultant Medical Ophthalmologist, St Thomas's Hospital, London.
Professor C.E.M. Griffiths	Professor of Dermatology, School of Medicine, Manchester University.
Dr L.K. Harding	Consultant in Nuclear Medicine, Dudley Road Hospital, Birmingham and Chair of the Radioactive Substances Advisory Committee.
Professor P.D. Home	Professor of Diabetes Medicine, Newcastle University.
Professor S.B. Kaye	Professor of Medical Oncology, Beatson Laboratories, University of Glasgow.
Dr R.H. Kimberlin	Scrapie and Related Diseases Advisory Service (SARDAS), Edinburgh.
Miss Gillian C.L. Lachelin	Reader and Consultant Obstetrician and Gynaecologist, University College and Middlesex School of Medicine.
Dr J.R. Larke	Senior Lecturer in Ophthalmic Optics, Department of Optometry and Vision Sciences, University of Wales.
Dr R.F.A. Logan	Senior Lecturer in Clinical Epidemiology and Consultant Physician, University Hospital, Nottingham.

External Advisory Panel contd.

Professor W.I. McDonald	Professor of Clinical Neurology, The National Hospital, London and President of the Association of British Neurologists.
Professor I.G. McKeith	Professor of Old Age Psychiatry, Newcastle General Hospital.
Mr B.J. Meakin	Senior Lecturer in Pharmaceutics and Executive Principal, Centre for Drug Formulation Studies, School of Pharmacy and Pharmacology, University of Bath.
Dr Elizabeth Miller	Head, Immunisation Division PHLS Communicable Diseases Surveillance Centre, London.
Dr Harriet C. Mitchison	Consultant Gastroenterologist, Royal Infirmary, Sunderland.
Dr Celia Moss	Consultant Dermatologist, The Birmingham Children's Hospital.
Dr G.D. Murray	Professor of Medical Statistics, Edinburgh University.
Professor J. Newsom-Davis	Professor of Clinical Neurology and Head of Department of Clinical Neurology, Oxford University.
Professor G. Nuki	Professor of Rheumatology, Edinburgh University.
Miss Jennifer M. Pinder	General Dental Practitioner, London.
Professor D.E. Poswillo	(Formerly) Professor of Oral and Maxillofacial Surgery, Guy's Hospital.
Dr C.J. Powell	Senior Lecturer in Toxicology, Department of Toxicology, St Bartholomew's & Royal London School of Medicine & Dentistry.
Professor J.M. Ritter	Professor of Clinical Pharmacology and Head of Department of Pharmacological Sciences, Guy's and St. Thomas's Medical and Dental School.
Professor P.A, Routledge	Medical Director, Welsh Adverse Drug Reactions Scheme and Professor of Clinical Pharmacology, University of Wales College of Medicine.
Professor C.A. Seymour	Professor of Clinical Biochemistry and Metabolic Medicine, St George's Hospital Medical School, University of London.
Professor of R.A. Seymour	Professor of Restorative Dentistry, Newcastle Dental School.
Dr Pamela J. Shaw	Senior Lecturer and Honorary Consultant in Neurology, School of Neurosciences, Newcastle University.
Dr R.J. Shearer	Consultant Urologist and Medical Director, The Royal Marsden NHS Trust.

External Advisory Panel contd.

Professor K. Sikora	Professor of Clinical Oncology, Hammersmith Hospital, London.
Dr Patricia O. Skacel	Senior Lecturer in Transfusion Medicine and Honorary Consultant Haematologist, Royal Post Graduate Medical School, Hammersmith Hospital, London.
Professor S.D. Shorvon	Professor of Neurology, National Hospital for Neurology and Neurosurgery, London.
Dr P.C. Conamore Smith	Director of Services for Women, Parkside NHS Trust London.
Professor Anne E. Tattersfield	Professor of Respiratory Medicine, Nottingham University.
Dr A.E. Theobald	Deputy Head of Department of Pharmacy, Kings College, London University.
Dr R. Thorpe	Head of Immunobiology, National Institute for Biological Standards and Control.
Mr T.D. Turner	Director, Surgical Dressings Research Unit, The Welsh School of Pharmacy, University of Wales College of Cardiff.
Professor N.J. Wald	Professor of Environmental & Preventive Medicine, Wolfson Institute of Preventive Medicine, St Bartholomew's Medical College, University of London.
Dr R.G. Will	Consultant Neurologist, National Creutzfeldt-Jakob Disease Surveillance Unit, Western General Hospital, Edinburgh.
Dr K.L. Woods	Reader in Therapeutics, Leicester University.
Professor E.G. Woodward	Head of Department and Professor of Optometry and Visual Science, The City University, London.
Dr P.L. Yap	Consultant, Edinburgh and South East Scotland Regional Blood Transfusion Centre, Royal Infirmary, Edinburgh.

Members of the British Pharmacopoeia Commission (1997).[7]

D. Ganderton (Chairman)	Visiting Professor of Pharmaceutics, University of London.
D.H. Callam (Vice- Chairman)	European Co-ordinator, National Institute for Biological Standards and Control.
W.G. Allen	Veterinary Surgeon
J.J. Ayres	A Director of Technical Operations in the Pharmaceutical Industry.
A.F. Fell	Professor of Pharmaceutical Chemistry, University of Bradford.
J.A. Goldsmith	Visiting Professor, University of Strathclyde, formerly a Director of Technical Operations in the Pharmaceutical Industry.
A.M.T. Lee	Member of the Veterinary Medicines Directorate
J.M. Midgley	Professor of Pharmaceutical and Medicinal Chemistry, Department of Pharmaceutical Sciences, University of Strathclyde.
A.C. Moffat	Director, Department of Pharmaceutical Sciences, Royal Pharmaceutical Society of Great Britain.
L.E. Ramsay	Consultant Physician, Royal Hallamshire Hospital; Professor of Clinical Pharmacology and Therapeutics, University of Sheffield.
N. Randall	A Director of Quality Assurance in the Pharmaceutical Industry.
G.D. Rees	A Manager of Quality Assurance in the Pharmaceutical Industry.
H.E.C. Worthington	Formerly a Head of Pharmacy, Research and Development in the Pharmaceutical Industry.
R.C. Hutton (Secretary and Scientific Director)	

[7]Medicines Commission et al (1997) p63.

Membership of the Committee for Proprietary Medicinal Products(1997)[8]

Professor J.M. Alexandre (Chairman)	Director, Agence du Medicament, Saint-Denis.
Dr E. Alhava [Finland]	Senior Medical Officer, National Agency for Medicines, Helsinki.
Professor F. de Andres-Trelles [Spain]	Professor of Pharmacology, Chairman of National Board of Drug Evaluation, Ministerio de Sanidad y Consumo, Madrid.
Professor J.M. Boeynaems [Belgium]	Professor of Pharmacology at the University Libre, Erasmus Hospital, Brussels.
G. De Greef [Belgium]	Pharmacist, Ministère de la Santé Publique, Brussels.
Professor M. Forte [Portugal]	Instituto da Farmacia e do Medicamento, Lisbon.
Profesor S. Garattini [Italy]	Istituto di Recherche, Milan
J. Genoux-Hames [Luxembourg]	Pharmacist and Inspector, Division de la Pharmacie et des Medicaments, Luxembourg.
Dr J. Guimaraes Morais [Portugal]	Associate Professor and Chairman of the Medical Committee, Instituto Nacional de Farmacia e do Medicamento, Lisbon.
Professor A. Hildebrandt [Germany]	Arzneimittel Professor für Pharmakologie und Toxicologie, Bundesinstitut für Arzneimittel und Medizinprodukte, Berlin.
H. Hovgaard (Vice-Chairman) [Denmark]	Director of Medicines Licensing Office, Danish Medical Agency, Brønshøj.
D. Jefferys [United Kingdom]	Head of Licensing Division, Medicines Control Agency, London.
Dr G. B. Jensen [Denmark]	Medical Superintendent, Danish Medicines Agency, Brønshøj.
Professor R. Kurth [Germany]	President and Professor, Paul-Ehrlich-Institut, Langen.
Dr P. Lecourtois [France]	Specialist in Public Health, Agence du Medicament, Saint-Denis.
Dr D. Lyons [Ireland]	Medical Assessor, Irish Medicine Board, Dublin.
Dr M. Marsellos [Greece]	University of Ioannina, Medical School, Department of Pharmacology.
O. Maranon [Spain]	Pharmacist, Ministerio de Sanidad y Consumo, Madrid.

[8]EMEA (1997b) pp20-21.

Membership of the Committee for Proprietary Medicinal Products contd.

Dr H. Pittner [Austria]	Associate Professor (Pharmacology and Toxicology) and Director, Federal Control Institute of Pharmacology, Vienna.
Dr J.L. Robert [Luxembourg]	Ingenieur and Chef de Division, Laboratoire National de Sante, Luxembourg.
Dr P. Sjöberg [Sweden]	Head of Division of Pharmacology, Medical Products Agency, Uppsala.
Professor K. Strandberg [Sweden]	Professor, Medical Products Agency, Uppsala.
Dr M. Teeling [Ireland]	Medical Assessor, Irish Medicine Board, Dublin.
Dr M.T. Toivonen [Finland]	National Agency for Medicines, Helsinki.
J.H. Trouvin [France]	Head of Unit (Biology/Biotechnology), Agence du Medicament, Saint-Denis.
Dr H. van Bronswijk [Netherlands]	Head of Department (Clinical Assessment), Medicines Evaluation Board, Rijswijk.
Dr W.F. van der Giesen [Netherlands]	Medicines Evaluation Board, Rijswijk.
Professor G. Vicari [Italy]	Professor and General Director, Instituto Superiore di Sanita, Rome.
Dr C. Wirthumer-Hoche [Austria]	National Institute for Quality Control of Drugs, Vienna.
Dr S. Wood [United Kingdom]	Director of Post-Licensing Division, Medicines Control Agency, London.
J. Yotaki [Greece]	Pharmacist and Director, National Drug Organisation, Holargos.

Members of the Management Board of the EMEA (1997)[9]

Mr Stefano Micossi [European Commission]	Directeur Général DG III.
Mr Fernando Mansito Caballero [European Commission]	Directeur Général Adjoint DG VI.
Professor Gianmartino Benzi [European Parliament]	Professor of Pharmacology, Instituto di Farmacologia.
Dr Dietrich Henschler [European Parliament]	Professor of Toxicology, Institut für Toxicology.
Dr Alexander Jentzsch [Austria]	Ministerialrat, Leiter der Gruppe Pharmazeutische Angelegenheiten, Budesministerium für Gesundheit, Sport und Konsumentenschutz.
Dr Ernst Luszczak [Austria]	Ministerialrat, Bundesministerium für Gesundheit, Sport und Konsumentenschutz.
J.P. Deroubaix [Belgium]	
M. Chojnowski [Belgium]	
I. Valsborg [Denmark]	
B. Lumholtz [Denmark]	
K. Leppo [Finland]	
Mr Hannes Wahlroos [Finland]	Director-General, National Agency for Medicines.
Monsieur Tabuteau [France]	Directeur Général, Agence Française du Médicament.
Dr Boisseau [France]	Directeur, Laboratoire National des Médicaments Vétérinaires.
G.J. Kothmann [Germany]	
MDg Dr H. Pabel [Germany]	Ministerialdirigent, Bundesministerium für Gesundheit.
G. Kavvadias [Greece]	
Mr Nikolaos Kokkolis [Greece]	Aristotelian University, Faculty of Veterinary Medicines, Department of Physiology.
J.A. Costelloe [Ireland]	

[9]Ibid p16. Unfortunately, the full designation has not been given for each of the members of the Board.

Members of the Management Board of the EMEA contd.

Mr Tom Mooney [Ireland]	Assistant Secretary, Department of Health.
V. Silano [Italy]	
Mr Romano Marabelli (Vice-Chairman) [Italy]	Direttore Generale Servizi Veterinari, Ministero della Sanità.
Madame Mariette Mackes-Lies [Luxembourg]	Inspecteur Chef de Division, Ministère de la Santé, Division Pharmacie et Médicaments.
Dr A.W. Broekmans [The Netherlands]	Directeur College ter Beoordeling van Geneesmiddelen van het Ministerie van W.V.C.
C. Van der Meijs [The Netherlands]	
M.A. Miranda [Portugal]	
Mr José Aranda da Silva [Portugal]	Presidente do Conselho de Administraçao de Infarmed.
A.M. Naveira [Spain]	
V. Almansa Sahagun [Spain]	
Ms B. Bratthall [Sweden]	Senior Health Officer, Department of Health, Ministry of Health and Social Affairs.
Dr A. Broström [Sweden]	Director, Medicinal Products Agency.
Mr S. Heppell (Chairman) [United Kingdom]	Deputy Secretary, Department of Health.
M. Rutter [United Kingdom]	
Dr K. Jones	Chief Executive, Medicines Control Agency, London.

Members of the Advisory Board on the Registration of Homeopathic Medicinal Products (1997).[10]

Dr Brain J. Kirby	Consultant Physician and Deputy Director Postgraduate Medical School, Exeter University.
Dr Gene S. Feder	Senior Lecturer, St Bartholomew's and the London Hospital Medical College, and part-time GP.
Dr Peter A.G. Fisher	Consultant Physician, Royal London Homeopathic Hospital.
Professor Andreas J. Geschler	Professor of Biochemical Toxicology, MRC Toxicology Unit, Leicester University.
Mr Francis E. Hunter	Veterinary Surgeon, West Sussex.
Dr Georgina H. Jolliffe	(Formerly) Senior Lecturer in Pharmacognsy, King's College.
Dr Steven B. Kayne	Community Pharmacist, Glasgow.
Ms Felicity E. Lee	Homeopathic Practitioner, Cardiff.
Dr David M. Lewis	Consultant Paediatrician, Bronglais General Hospital, Aberystwyth.
Dr Eileen M. Scott	Senior Lecturer, School of Pharmacy, The Queens University, Belfast.
Mr John R. Tindall	Veterinary Consultant, Kent.

[10] Medicines Commission et al (1997).

Appendix XV

Important Matters Considered by the Medicines Commission (1969 - 1997)

The information in this list is extracted from the Annual Reports of the Medicines Commission (1969 - 1997). The year when each matter was discussed is given in brackets.

- *The legal status of medicinal products [1970], [1971], [1972] [1974] [1977], [1981], [1982], [1983], [1985], [1986], [1989], [1990], [1992], [1993], [1994], [1995] and [1996]*
- *The European Pharmacopoeia [1970]*
- *The European Free Trade Association Convention on Mutual Recognition of Pharmaceutical Inspections [1970]*
- *Labelling and leaflets [1971], [1986], [1988], [1990] and [1993]*
- *Deaths linked to a batch of contaminated intravenous infusion fluids [1972] and [1973]*
- *The "unintentional passage of commercially confidential material" between the Committee on Safety of Medicines and the British Pharmacopoeia Commission [1972]*
- *Experiments using animals [1973], [1979] and [1983]*
- *Child safety [1973], [1974], [1975], [1977], [1979], [1980], [1981], [1987] and [1993]*
- *The identification of medicinal products [1973], [1979] and [1983]*
- *Bioavailability of medicinal products [1973] and [1975]*
- *Data sheet regulations [1971], [1972], [1973], [1981] and [1986]*
- *The Committee of Enquiry into the Regulation of the Medical Profession [1973]*
- *The restriction on the sale or supply of phenacetin [1974] and [1994]*
- *Product liability [1974], [1977] [1978], [1979] and [1980]*
- *Press publicity regarding the naming of medicinal products in cases of misuse. [1974]*
- *Information to patients about medicinal products [1975], [1976] [1977], [1978], [1980] and [1986]*
- *Information for doctors about medicinal products [1975] and [1986]*
- *The control of tobacco substitutes and additives within the legislative framework of the Medicines Act [1975] and [1976]*
- *Herbal and other traditional medicinal products [1976], [1981] and [1985]*
- *Hazardous medicinal products [1976] and [1977]*
- *Homeopathic medicinal products [1976], [1987], [1990], [1991], [1992] and [1993]*
- *The free movement of medicinal products within the European Community [1976], [1979], [1980], [1982], [1987], [1988] [1989], [1990], [1991], [1992], [1993] and [1994]*
- *The establishment of the Committee on Proprietary Medicinal Products [1976]*
- *Royal Commission on the National Health Service [1976]*
- *Devolution to Scotland and Wales [1976]*
- *Oral contraceptives [1977]*
- *EC Directive on Radiological Protection (76/579 Euratom) [1977]*
- *EC Directive on Colouring Matters [1977]*
- *The advertising of medicinal products [1977], [1990], [1991]*
- *Parenteral administration of medicinal products by non-statutorily registered practitioners [1978], [1979] and [1980]*
- *Restrictions on medicinal products containing chloroform [1978]*
- *Traditional Indian medicines containing lead and other heavy metals [1979]*

- *Original pack dispensing [1979] and [1985]*
- *Clinical Trial Certificates [1980]*
- *Healthy volunteers participating in clinical trials [1980], [1984] [1985], [1986], [1988] and [1989]*
- *The Sunningdale Conference "to mark the ten-year stage in the operation of the present licensing system in the United Kingdom" [1981]*
- *Advice from pharmacists to the public regarding medicinal products [1981]*
- *Medicines Division Symposium [1982]*
- *Parallel importing [1982], [1983] and [1984]*
- *Contact lens products [1982], [1983] and [1993]*
- *Prescribing of medicinal products which had been withdrawn [1984]*
- *Limits on the range of medicinal products prescribable under the NHS and the possibility to advertise prescription only medicines directly to the public [1985]*
- *The legal liability of the Medicines Commission [1985]*
- *Disclosure of members' interests in the pharmaceutical industry [1985] and [1986]*
- *European regulation of high technology medicinal products [1985] and [1986]*
- *The regulation of medical devices [1986], [1989], [1990], [1992] and [1994]*
- *Information to pharmacists [1986]*
- *The "Study of Control of Medicines" by Cunliffe and Evans [1987] and [1988]*
- *The legal status of sympathomimetic eye drops [1988]*
- *Post-marketing surveillance [1988] and [1994]*
- *Forged prescriptions [1988]*
- *The development of good clinical practice guidelines [1989]*
- *The establishment of the Medicines Control Agency [1989] and [1990]*
- *Prescribing by nurses [1990], [1992] and [1994]*
- *The "Rational Use of Medicines" consisting of European proposals relating to wholesale distribution, classification of human medicines, labelling and leaflets [1990] and [1991]*
- *EC "Extension Directives" [1991]*
- *EC Advisory Working Group on Inspection and Quality Control [1991]*
- *Good Manufacturing Practice [1991] and [1992]*
- *The Medicines Information Bill [1992] and [1993]*
- *The first International Conference on Harmonisation of technical requirements for the registration of pharmaceuticals for human use in Japan, USA and the European Community [1992]*
- *The National Consumer Council's report "Balancing Acts: conflicts of interest in the regulation of medicine" [1993]*
- *The establishment of the Gene Therapy Advisory Committee [1993]*
- *The work of the MCA's Medicines Inspectorate regarding wholesalers and manufacturers [1994]*
- *Bovine Spongiform Encephalopathy (BSE) [1996]*
- *Proposals by the Department of Health to streamline the system of Ethics Committee review of multi-centre health-related research [1996]*
- *Human suspected adverse reactions to veterinary medicines [1996]*
- *Adverse reactions to dietary supplements and traditional remedies [1996]*

Appendix XVI

"Matters of Medical and Pharmaceutical Relevance" commented on by the CSM (1971 - 1997)

- *Policy regarding efficacy in relation to the assessment of evidence submitted with licensing applications [1971] and [1972]*
- *Safety of Medicines Advisers [1972]*
- *Ethical aspects of clinical trials [1973]*
- *Toxicity studies performed outside the UK [1973]*
- *Implementation of Directive 65/65/EEC [1973]*
- *Test marketing of revised formulation of a medicinal product [1973]*
- *Desiccants and cushioning in packs of medicinal products [1973]*
- *Warning cards issued to patients [1973]*
- *Legal status of medicinal products [1973], [1974], [1993], [1995] and [1996]*
- *Advertising [1973] and [1974]*
- *Delays in the processing of licensing applications [1973], [1974] and [1975]*
- *The marking of medicinal products as "recently introduced" [1974] and [1975]*
- *Maternal drug histories in babies with congenital abnormality [1974]*
- *Declaration of alcohol in medicinal products [1974]*
- *The labelling of monocompetent insulins [1974]*
- *Notes for guidance on reproduction studies [1974]*
- *Conference on Dissemination of Information [1975]*
- *The safety and efficacy of traditional remedies [1975]*
- *Carcinogenicity studies [1975], [1976] and [1995]*
- *Compendium of Standards for Biological Medicinal Products [1976]*
- *Clinical trials [1976]*
- *Compensation for volunteers to clinical trials and the Pearson Commission [1978]*
- *International Conference on the Beagle Bitch as a Carcinogenicity Model for the testing of Progestogens [1979]*
- *Bioequivalence and stability [1981]*
- *Drug use in the elderly [1983]*
- *New guidelines for the data requirements of sustained release theophylline preparations [1985]*
- *The screening of all donations of blood products for HTLV-III [1985]*
- *Bovine Spongiform Encephalopathy [1988], [1989] and [1996]*
- *Mineral hydrocarbons in licensed medicines [1993]*
- *Clinical trials of gene therapy [1993]*
- *Dose response information to support drug registration [1993]*
- *Genotoxicity [1993]*
- *Reproductive toxicity [1993]*
- *Studies in support of special populations (geriatrics) [1993]*
- *The use of surrogate markers in the licensing of drugs for HIV infection [1993]*
- *Replacement of chlorofluorocarbons (CFCs) in metered dose inhalation products [1993]*
- *Categorisation of medicinal products for use in pregnancy [1993]*

- *Antidementia drugs [1993]*
- *Medicines and children [1994]*
- *CPMP guideline on cardiovascular drugs [1995]*
- *CPMP guideline on viral validation and plasma derived medicinal products [1995]*
- *Creutzfeldt-Jakob disease and plasma derived blood products [1995]*
- *Anti-HIV medicinal products [1996]*
- *CPMP guideline on sterile products [1996]*
- *CPMP guideline on non-clinical testing of old substances [1996]*
- *CPMP guideline regarding viral safety evaluation of biotechnology products [1996]*

Appendix XVII

A Typical Monograph from the British Pharmacopoeia 1993

Aspirin [Acetylsalicylic Acid]

NOTE: The name Aspirin may be used freely in many countries including the United Kingdom. In countries where exclusive proprietary rights in this name are claimed, the official title is Acetylsalicylic Acid.

Definition

Aspirin is *O*-acetylsalicylic acid. It contains not less than 99.5% and not more than 101.0% of $C_9H_8O_4$ calculated with reference to the dried substance.

Characteristics

Colourless crystals or a white crystalline powder; odourless or almost odourless. It melts at about 143°, Appendix V A, Method VI. Slightly soluble in *water*, freely soluble in *ethanol* (96%);soluble in *chloroform* and in *ether*.

Identification

Test A may be omitted if tests B, C and D are carried out. Tests C and D may be omitted if tests A and B are carried out.

A. The infrared absorption spectrum, Appendix IIA, is concordant with the spectrum of *acetylsalicylic acid EPCRS*.

B. Heat 0.2g to boiling for 3 minutes with 4ml of 2M *sodium hydroxide* , cool add 5ml of 1M *sulphuric acid* and filter. The melting point of the precipitate, after wahing and drying at 100° to 105° is 156° to 161°, Appendix V A, Method I.

C. Mix 0.1g with 0.5g of *calcium hydroxide* and heat; the fumes produced gradually turn *nitrobenzaldehyde paper* yellowish green or bluish green. Moisten the paper with 2M *hydrochloric acid*; the clour changes to blue.

D. Heat about 20mg of the precipitate obtained in test B with 10ml of *water* and cool. The resulting solution yields reaction A characteristic of *salicylates*, Appendix VI.

Clarity and Colour of Solution

A solution of 1.0g in 9ml of *ethanol* (96%) is clear, Appendix IV A, and *colourless*, Appendix IVB, Method II.

Heavy Metals

Dissolve 0.75g in 9ml of *acetone* and dilute to 15ml with *water*. 12ml of the solution complies with *limit test B for heavy metals*, Appendix VII. Use a solution prepared by diluting *lead standard solution (100 ppm Pb)* with a mixture of 9 volumes of *acetone* and 6 volumes of *water* to contain 1μg of Pb per ml as the standard (20 ppm).

Salicylic Acid

Dissolve 0.1g in 5ml of *ethanol* (96%) and add 15ml of iced *water* and 0.05ml of a 0.5% w/v solution of *iron (III) chloride hexahydrate*. After 1 minute the colour of the solution is not more intense than that of a solution prepared at the same time by adding a mixture of 4ml of *ethanol* (96%), 0.1ml of 5M acetic acid, 15ml of *water* and 0.05ml of a 0.5% w/v solution of w/v solution of *iron (III) chloride hexahydrate* to 1ml of 0.0050% w/v solution of *salicyclic acid* in *ethanol* (96%)(500ppm).

Related Substances

Dissolve 0.15g in 10ml of 0.1M *tetrabutylammonium hydroxide* in *propan-2-ol* and allow to stand for 10 minutes. Add 8ml of 0.1M *hydrochloric acid* and 20ml of a 1.9% w/v solution of *sodium tetraborate* and mix. Add with constant swirling 2ml of a 1% w/v solution of *dimethylaminoantipyrine* and 2ml of 1% w/v solution of *potassium hexacyanoferrate (III)*. After 2 minutes dilute to 100ml with *water* and allow to stand for 20 minutes. The absorbance at 505 nm of a 2-cm layer of the resulting solution is not more than 0.25, Appendix IIB (about 0.1% expressed as aspirin).

Loss on Drying

When dried to constant weight over phosphorus pentoxide at a pressure of 1.5 to 2.5 kPa, loses not more than 0.5% of its weight. Use 1g.

Sulphated Ash

Not more than 0.1%, Appendix IX A, Method II. Use 1g.

Assay

Dissolve 1g in 10ml of *ethanol* (96%), add 50ml of 0.5m *sodium hydroxide VS*, stopper the flask and allow to stand for 1 hour. Add 0.2ml of *phenolphthalein solution* and titrate with 0.5m *hydrochloric acid VS*. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of sodium hydroxide required. Each ml of 0.5m *sodium hydroxide VS* is equivalent to 45.04mg of $C_9H_8O_4$.

Storage

Aspirin should be kept in an airtight container. It is stable in air but in contact with moisture it is gradually hydrolysed to acetic and salicylic acids.

Preparations

Aspirin
Dispersible Aspirin Tablets
Effervescent Soluble Aspirin Tablets
Aspirin and Caffeine Tablets
Co-codaprin Tablets
Dispersible Co-codaprin Tablets

Action and use Analgesic; antipyretic.

Thetitle of the monograph in the European Pharmacopoeia is Acetylsalicylic Acid.

Appendix XVIII

Medicinal Products which have been granted a Community Marketing Authorisation under the Centralised Procedure (1995-1997)

Product [list A or B] ***Manufacturer [Country]***	**Therapeutic Area**	**Time Taken** **[Clock stopped]**
Gonal-F (follitropin-alpha) [A] Serono Laboratories [IT/CH]	Treatment of Infertility	107 days [30 days]
Betaferon (interferon beta-1b) [A] Schering AG [DE]	Immuno-stimulation Multiple sclerosis	138 days [55 days]
Taxotere (docetaxel) [B] Rhône-Poulenc Rorer [FR]	Cytotastic	100 days [93 days]
NovoSeven (factor VIIa) [A] Novo-Nordisk [DK]	Coagulation factor	210 days [80 days]
CellCept (mycophenolate mofetil) [B] Hoffmann-La Roche [CH]	Prevention of kidney transplant rejection	243 days [47 days]
Fareston (toremifene) [B] Orion	Treatment of certain breast tumours	240 days [50 days]
Humalog (insulin lispro) [A] Lilly Industries [USA]	Diabetes mellitus	245 days [81 days]
Puregon (follitropin-beta) [A] Organon [NL]	Infertility treatment	203 days [151 days]
Zerit (stavudine) [B] Bristol Myers Squibb [UK]	second line mono-therapy of HIV infection	150 days
Rilutek (riluzole) [B] Rhône-Poulenc Rorer [FR]	Amyo-trophic lateral sclerosis	161 days [41 days]
Caelyx (doxorubicin-HCl) [B] Sequus Pharmaceutical Inc [UK]	AIDS-related Kaposi's Sarcoma	222 days [150 days]
Bondronat (ibandronic acid) [B] Boehringer Mannheim [DE]	Hyper-calcemia of malignancy	203 days [52 days]
Bonviva (ibandronic acid) [B] Galenus Mannheim [DE]	Hyper-calcemia of malignancy	203 days [52 days]
Tritanrix (combined vaccine) [A] SmithKline Beecham [BE]	Hapatitis B and DPT vaccine	180 days [240 days]

Product [list A or B] ***Manufacturer [Country]***	**Therapeutic Area**	**Time Taken** **[Clock stopped]**
Epivir (lamivudine) [B] Glaxo-Wellcome [UK]	Combination treatment of HIV	150 days [105 days]
CEA-Scan (arcitumomab) [A] immuno-medics [USA]	Diagnosis of colonic and rectal carcinoma	110 days [386 days]
Tecnemab K 1 (anti-melanoma antibody) [A] Sorin [I]	Visualisation of cutaneous melanoma lesions	187 days [320 days]
Rapilysin (reteplase) [A] Boehringer Mannheim [DE]	Thrombolytic therapy of acute myocardial infarction	204 days [83 days]
Ecokinase (reteplase) [A] Galenus Mannheim [DE]	Thrombolytic therapy of acute myocardial infarction	204 days [83 days]
Twinrix adult (combination vaccine) [A] SmithKline Beecham [BE]	Vaccine for immunisation against hepatitis A and B	197 days [83 days]
Norvir (ritonavir) [B] Abbott [USA]	Combination treatment of HIV	69 days
Indimacis 125 (igovomab) [A] CIS bio international	Diagnosis of ovarian adenocarcinoma	154 days [363 days]
Invirase (saquinavir) [B] Hoffmann-La Roche [CH]	Treatment of Zidovudine-exp. patients with advanced HIV disease	180 days [80 days
Zyprexa (olanzapine) [B] Eli Lilly [USA]	Antipsychotic	198 days 56 days
Olansek (olanzapine) [B] Eli Lilly [USA]	Antipsychotic	198 days 56 days
Crixivan (indinavir) [B] Merck Sharp & Dohme [USA]	Treatment of patients with AIDS	85 days 12 days
Hycamtin (topotecan) [B] SmithKline Beecham	Ovary metastatic carcinoma	154 days 28 days
Evotopin (topotecan) [B] Beecham Group [USA}	Ovary metastatic carcinoma	154 days 28 days

Product [list A or B] ***Manufacturer [Country]***	**Therapeutic Area**	**Time Taken** **[Clock stopped]**
LeukoScan [A] Immuno-medics [USA]	Diagnostic agent	210 days [183 days]
Insuman (human insulin) [A] Hoechst AG [DE]	Diabetes mellitus	158 days [182 days]
Twinrix paediatric (combined vaccine) [A] SmithKline Beecham [BE}	Immunisation against Hepatitis A/B in children	132 days [35 days
Vitrasert implant (ganciclovir) [B] Chrion [USA]	Treatment of CMV renititis in patients with AIDS	183 days [119 days]
Avonex (interferon beta) [A] Biogen [USA]	Immunostimulating agent	216 days [307 days]
Refludan (lepirudin) [A] Behringwerke AG [DE]	Anti-coagulation therapy for heparin-associated thrombocytopenia	200 days [112 days]
Vistide (cidofovir) [B] Gilead [USA]	Treatment of CMV renititis in pateint with AIDS	209 days [112 days]
Liprolog Biolysprol (insulin lispro) [A] Lilly Industries [USA]	Diabetes mellitus	48 days
Teslascan (mangafodipir) [B] Nycomed [NO]	Detection and characterisation of liver lesions	171 days 27 days
Cystagon (cysteamine) [B] Orphan Sarl [FR]	Nephropathic lesions	176 days [181 days]
Orlaam (levacetylmethadol) [B] BRI International [BE]	Substitution maintenance treatment of opiate addiction	201 days 487 days
Revase (desirudin) [A] Ciba-Geigy [CH]	Antithrombotic	181 days [398 days]
NeoRecormon (epoetin beta) [A] Boehringer Mannheim [DE]	Antianaemic	209 days [140 days]
Infanrix-HepB (DTPa-HB vaccine) [A] SmithKline Beecham Biologicals [USA]	Active immunisation of infants	199 days [217 days]

Product [list A or B] ***Manufacturer [Country]***	**Therapeutic Area**	**Time Taken** **[Clock stopped]**
Heliobacter Test INFAI (C-urea) [B] INFAI [DE]	Heliobacter pylori Test	162 days [28 days]
Tasmar (tolcapone) [B] Hoffmann-La Roche [CH}	Use in Parkinson's disease	170 days [90 days]
Benefix (monacog alpha) [A] Genetics Institute [USA]	Haemophilia B, factor IX deficiency	162 days [55 days]
Karvea (irbesartan) [B] Sanofi BMS SNC [FR]	Treatment of hypertension	163 days [27 days]
Sifrol (pramipexole) [B] Boehringer Ingelheim [DE]	Treatment of idiopathic Prkinson's disease	

Appendix XIX

Directives Bulletins, Device Bulletins, Hazard Notices and Safety Notices issued by the Medical Devices Agency

Directives Bulletins (1992 - 1997)

Bulletin No. 1 [March 1992]	Information for Manufacturers.
Bulletin No. 2 [1992]	The CE Mark.
Bulletin No. 3 [August 1992]	The Vigilance System. Update on the Directives.
Bulletin No. 4 [December 1992]	Conformity Assessment Procedures.
Bulletin No. 5 [1993]	Pre-clinical Assessment Procedures. The Product Registration Scheme.
Bulletin No. 6 [March 1993]	The Notified Body.
Bulletin No. 7 [April 1993]	The Competent Authority.
Bulletin No. 8 [April 1993]	Information about the EC Medical Devices Directives.
Bulletin No. 9 [August 1993]	The Citizen's Charter and Deregulation. A Code for Enforcement.
Bulletin No. 10 [September 1993]	The Classification Rules.
Bulletin No. 11 [June 1994]	EC and EFTA Member States. The EEA Agreement and the EC Medical Devices Directives.
Bulletin No. 12 [November 1994]	Sale and Supply of In Vitro Diagnostic Devices.
Bulletin No. 13 [November 1994]	Standards.
Bulletin No. 14 [December 1994]	Compliance Cost Assessments.
Bulletin No. 15 [May 1995]	The Medical Devices, Electromagnetic Compatibility and Low Voltage Directives.
Bulletin No. 16 [May 1995]	Information about Packaging and the Packaging Waste Directive.
Bulletin No. 17 [May 1995]	Medical Devices and Medicinal Products.
Bulletin No. 18A [August 1996]	The Medical Devices Regulations: Implications on Healthcare and other Related Establishments.
Bulletin No. 19 [August 1996]	Own Brand Labelling and Rented Products.

Device Bulletins issued by the MDA (1995-1997)

1997
DB 9703 Selection and use of infusion devices for ambulatroy applications. April 1997 DB 9702 Electromagnetic compatability of medical devices with mobile communications. March 1997 Summary DB 9701 Adverse Incident Reports 1996. February 1997
1996
DB 9607 Decontamination of endoscopes. November 1996 DB 9606 Wheelchair and vehicle passenger safety lifts : Safe working practices. October 1996 DB 9605 The purchase operation and maintenance of benchtop steam sterilizers. June 1996 DB 9604 Withdrawal of MLQ forms - England. June 1996 DB 9603 Adverse Incident Report 1995. April 1996 DB 9602 Guidance on the safe use of lasers in medical and dental practice. April 1996 DB 9601 Latex sensitisation in the health care setting (use of latex gloves). April 1996
1995
DB 9505 Symbols used on medical devices and their packaging. December 1995 DB 9504 The management of infusion systems - A report by the Scottish Home Office and Health Department. November 1995 DB 9503 Infusion systems. May 1995 DB 9502 Product approved scheme for sterile single use plastics administration sets and air inlet assemblies. January 1995 DB 9501 The reuse of medical devices supplied for single use only. January 1995

Hazard Notices issued by the MDA (1995-1997)

1997
IIN(97)12 Electrically heated mattress, KanMed Operatherm Control Unit Type : OP-200-020. September 1997[Image]
IIN(97)11 Bed Side Rails (Cot Sides) - Risk of Entrapment. August 1997
IIN(97)10 Lead Aprons, Gonad Shields & Thyroid Collars used for x-ray shielding. June 1997
IIN(97)9 Epidural Catheters, Minipacks, and Regional Anaesthesia trays. June 1997
IIN(97)8 Shelf Pessary (Also known as Simpson Pessary) All sizes. May 1997
IIN(97)7 4F Umbilical Cannula. April 1997
IIN(97)6 Bone Substitute : Unilab Surgibone. April 1997
IIN(97)5 Ohmeda Standard Airway Adaptor. April 1997
IIN(97)4 Unilab Surgibone Bone Substitute. April 1997
IIN(97)3 Baxter Healthcare sterile blood administration sets. April 1997
IIN(97)2 Collapsible intravenous fluid containers. March 1997
IIN(97)1 Anthcor Permanent Vena Cava Filters 'Standard' and 'Large': Catalogue numbers; 50-109, and 50-110. January 1997
1996
IIN(96)12 Nursing and Transport Incubators. August 1996
IIN(96)11 2.5mm Tracheal Tube and Holder Kit. July 1996
IIN(96)10 Ohmeda Tec 6 Desflurane Anaesthetic Vaporizer; Mains Lead. July 1996
IIN(96)9 In-house manufactured spirit level used in Central Venous Pressure (CVP) measurement. July 1996
IIN(96)8 Breathing systems filters. July 1996
IIN(96)7 Silicone fluid for body contouring. June 1996
IIN(96)6 Phototherapy devices for the treatment of neonates and infants. June 1996
IIN(96)5 Gambro renal dialysis blood monitors type. June 1996
IIN(96)4 Wooden Tongue Depressor. May 1996
IIN(96)3 Abbott Diagnostic's IMX HIV-1, HIV/2 3 Generation Plus Assay. April 1996

1996 contd.
HN(96)2 GU2821 7mm Insulated Cannula. GU2838 5mm Insulated Cannula. March 1996
HN(96)1 Akers Laboratories Inc. "Health Test" Anti-HIV 1-2 test. February 1996
1995
HN(95)6 Graseby Medical MS16, MS16A and MS26 Ambulatory Syringe Pumps. November 1995
HN(95)5 Intra-oral X-ray Units 70-X, IRIX 70-C, IRIX 70-E. August 1995
HN(95)4 MSV Renalchair 100 and DT Comfort Chairs. June 1995
IIN(95)3 Handpieces used in Phaco microsurgical procedures and their reusable accessories. May 1995
IIN(95)2 Hip Implants : CPT Femoral Stems 8011 et seq; LCO Femoral Stems 8012 et seq; CMTA Femoral Stems 8020-001 to 8020-005. May 1995
IIN(95)1 "BONELOC" Bone Cement : Catalogue No 402202 - Boneloc Vacuum Pac Cement Small 50gm; Catalogue No 402204 - Boneloc Vacuum Pac Cement Standard 80gm; Catalogue No 401180 - Boneloc Vacuum Pac Cement Standard 90gm. April 1995

Safety Notices issued by the MDA (1995-1997)

1997
SN 9712 Harrogate Shower Chair. Incorrect Positioning of Seat Securing Clips. September 1997[Image]
SN 9711 Ivac 597 and 598 Infusion Pump. August 1997
SN 9710 Phacoemulsification: risk of corneal damage. July 1997
SN 9709 Bath and shower seating equipment : Risk of injury. May 1997
SN 9708 Reusable multi-well slides and tiles : Risk of contamination due to inappropriate washing procedures. May 1997
SN 9707 Arjo shower trolley : Risk of side rails failure due to corrosion. May 1997
SN 9706 Mobile Communications : Interference with Medical Devices. April 1997Summary
SN 9705 Pisces Bath Lifter: Huntleigh Community Care. February 1997
SN 9704 Rad-Sure Blood irradiation indicator labels 25 Gy manufactured by ISP and distributed by Field Emission. February 1997
SN 9703 Tympanic Thermometer - Sherwood Genius - Guidelines to reduce the risk of incorrect temperature readings. January 1997
SN 9702 Batteries used in critical care devices. January 1997
SN 9701 Reporting Adverse Incidents relating to Medical Devices. January 1997

1996

SN 9640 Infusion Pumps : IVAC 770 Syringe Pumps : Incorrect dosage rate display. December 1996

SN 9639 Nursing Incubators : Vickers Medical models 59 & 79. December 1996

SN 9638 Alton Dean Pressure Infusors : Potential door failure. December 1996

SN 9637 Transfer and lifting equipment : Problems associated with moving patients. November 1996

SN 9636 Demountable anaesthetic agent vaporizers. November 1996

SN 9635 SES Matron steam sterilizers (autoclaves) - Eschmann equipment - Risk of overheating or fire. November 1996

SN 9634 HNBR Beacon tip cardiac catheters, Cook (UK) Ltd; Product recall of all batches supplied before October 1996. October 1996

SN 9633 Syringe Pump : Vickers Treonic IP3. October 1996

SN 9632 Bioket Toxocell Latex Test Kit (for the diagnosis of toxoplasmosis) Batch G3395 : Faulty batch. October 1996

SN 9631 Labotech automated analyser : Risk of sample contamination and carryover. October 1996

SN 9630 Emergency resuscitation kit with Pin Index Regulator F: 1Aerdal. September 1996

SN 9629 Howmedica International Inc : Polyethylene wear of the bearing surface of the 7mm resurfacing tibial components of the PCA primary knee prostheses. September 1996

SN 9628 Detachable mains supply leads for use with medical devices. Reported problems. September 96

SN 9627 Patient hoist : ARJO Ambulift - Sudden dropping of jib arm. September 1996

SN 9626 X-ray contrast media injectors : Risk of air embolism. September 1996

SN 9625 Infusion Pump : IVAC P Series Pumps Software Upgrade. August1996

SN 9624 Lung Ventilator : Ohmeda OAV 7750 : Potential Failure of Power Supply. August 1996

SN 9623 Newton products "Avon" wheelchairs - Risk of failure when carried on vehicles. August 1996

SN 9622 Spacelabs ECG monitors software fault recall. August 1996

SN 9621 Addendum to MDA SN 9611 Graseby MS 2000 Syringe Pump confusion over risk category. August 1996

SN 9620 Polyurethane coated breast implant : Continued implantation contrary to earlier advice. July 1996

SN 9619 Compatibility of medical devices and their accessories and reprocessing units with cleaning, disinfectant and sterilizing agents. July 1996

SN 9618 Mediclave or Medical Clave steam sterilizers - inadequate safety locks. July 1996

SN 9617 Zirconia Ceramic Heads for modular Total Hip Femoral Components: Advice to users on resterilization. June 1996

SN 9616 Extra-laboratory use of blood glucose meters and test strips :Contra-indications, training and advice to users. June 1996

SN 9615 Philip Medical Systems (PMS) CS Ceiling Suspensions. May 1996

SN 9614 Mavig Ceiling Suspended Radiation Shield - Model 6262. May 1996

SN 9613 X-ray equipment : Safety of footswitches used under adverse conditions. May 1996

SN 9612 Need for decontamination of blood gas analysers used in near-patient testing. May 1996

SN 9611 Graseby MS 2000 syringe pump confusion over risk category. May 1996

SN 9610 Pre - 1989 Eschmann Operation Tables : Potential failure of main hinge. March 1996

SN 9609 Risk of skin burns from lead adaptors used with electrosurgical equipment. March 1996

SN 9608 Arcpmedical Infusion Systems Ltd VP 5000 Series Pumps : Risk of electric shock from loose panel mounted mains connector. March 1996

SN 9607 Modification of Baxter Flo-gard Infusion Pumps. March 1996

SN 9606 Drager Oxylog Ventilator pressure relief valve risk of failure when autoclaved using the 134 degree centigrade cycle. February 1996

SN 9605 Powered wheelchairs fitted with Fracmo motors; possible brake defects. January 1996

SN 9604 Walking Aids - inspection and maintenance. January 1996

SN 9603 Risk of ignition of sealed polyester vascular grafts/patches. January 1996

SN 9602 Insufflators : Risk of contamination. January 1996

SN 9601 Reporting Adverse Incidents relating to medical devices. January 1996

1995

SN 9533 Bibby Sterilin "Venturi" Transport Swabs : Product Recall. December 1995

SN 9532 Marquette Responder 1200, 1250 and 1500 Defibrillator : Ni Cad battery recall. November 1995

SN 9531 Air Flow Incubators - Risk of injury to babies when the airflow is inadvertently obstructed or diverted. November 1995

SN 9530 Radcliffe Rehabilitation Services : Failures of Shadow Wheelbase. November 1995

SN 9529 Radcliffe Rehabilitation Services : Failure of MKII Shadow Wheelbase. November 1995

SN 9528 Medix Two-Pin Universal Mains Leads : Risk of electric shock. October 1995

SN 9527 Geka manufacturing Ltd - Endocervical Brushes - Risk of head detaching in use. October 1995

SN 9526 Graseby Medical MS16A and MS26 Ambulatory Syringe Pumps. October 1995

SN 9525 Howmedica International Inc : Fracture and fragementation of the large posterior cruciate retaining tibial component (6mm) of the Kinematic Total Knee replacement. October 1995

SN 9524 Wheelchair Battery Charger. October 1995

SN 9523 Wheelchairs - Removal and replacement of circlips. October 1995

SN 9522 Bayreuth Standing Frame - Failure of adjustment locks. September 1995

SN 9521 Zimmer Ltd - Fracture of the Acetabular Peg component of the Ring TCII hip prostheses. September 1995

SN 9520 Zimmer Ltd - Fracture of the femoral component of Ring TCII hip prostheses manufactured before march 1988. August 1995

SN 9519 Medic-Air Limited : Theramist Nebuliser Humidifier Part Nos. 3551 and 3551A suppliers recall. July 1995

SN 9518 Glucotide Blood Glucose Test Strips - Product recall. July 1995

SN 9517 Risk of burns to patients, with attached monitoring leads, undergoing MRI Scan. July 1995

SN 9516 Decontamination of medical devices and equipment prior to investigation, inspection, service or repair. July 1995

SN 9515 Fragmentation of instruments during phacoemulsification procedures. June 1995

SN 9514 Inspection and upgrade of YUASA NP24 batteries on Picker Explorer mobile x-ray machines. June 1995

SN 9513 ARJO Hygiene Chairs - Risk of patient entrapment. June 1995

SN 9512 IGE Senix/Senograph Mammography units - Bucky clips. May 1995

SN 9511 Picker International 'D' Series mobile x-ray machines recommended batteries must be used. May 1995

SN 9510 Picker 'Explorer' mobile x-ray units. May 1995

SN 9509 Marquette Responder 1250 and 1500 defibrillators : Upgrade to prevent memory failure and device lock-up. May 1995

SN 9508 Possible detachment of heater grid from the Vickers combined infant radiant warmer/resusataire due to failure of retaining clips. May 1995

SN 9507 Salford Swivel Walkers - Regular inspection and maintenance. May 1995

SN 9506 Hydrophillic coated guide wires - Stripping of coating: Risk of embolism. April 1995

SN 9505 Addendum to SAB(94)46 Breathing system hinged support arm failure. April 1995

SN 9504 Proper use of unfused 'Red Plugs' on mobile x-ray units. March 1995

SN 9503 Risk of fire when using defibrillators in an oxygen enriched atmosphere. February 1995

SN 9502 Addendum to SAB(94)16 Becton Dickinson Programme 1 and syringe pumps manufactured before 1990. Upgrade facility to high risk category requirements. February 1995

SN 9501 Henleys Medical Oxygen Connecting tubes. Manufacturers recall. January 1995

Appendix XX

"Highlights" of the Activities of the MDA (1995 - 1997)

Information taken from the Annual Reports of the MDA.

1995/96

- Processed 4,298 adverse incident reports - a 12% increase from 1994-95 - using less resources, through re-engineering the investigational procedure;
- Published and distributed 8 Hazard Notices, 40 Safety Notices and 7 Pacemaker Technical Notes;
- Reported 6 incidents to Member States under the vigilance system required by the Medical Devices Directives, receiving 12 in return;
- Assessed 56 proposals for the UK clinical investigation of new, low risk medical products and 48 for high risk ones, in an average of 32 and 49 days respectively.
- Agency staff made about 60 presentations on device safety and the UK Medical Devices Regulations at national and international conferences and seminars;
- Published and widely distributed :guidance on the safe use of lasers in medical and dental practice; the second part of a manual providing guidance on decontamination of medical devices returned to any area of hospital in which decontamination may be performed; and guidance on the transport of neonates;
- Published 121 device evaluation reports to the NHS and 17 on products for disabled people;
- Provided 3,010 answers in writing to enquiries concerning the Medical Devices Regulations, and responded to 2,154 requests for information packs, achieving virtually 100% Code of Practice level of service in both cases;
- Reached agreement with 8 Notified Bodies and 2 foreign certification organisations for the mutual recognition of quality assurance audits, thereby benefiting manufacturers and allowing the Agency to balance its resources better; and
- Contributed to the work of some 140 committees and working groups writing new European and International safety standards.

1996/97

- Processed 4330 adverse incident reports of which 43 involved fatalities and 45 serious injury; and published an analysis of the reports received during the 1996 calendar year;
- Published and distributed 12 Hazard Notices, 35 Safety Notices and 7 Pacemaker Technical Notes;
- Introduced new procedures to improve liaison with other parts of the Department of Health, the Press Office and Ministers to improve our response to incidents that alarm the public and the media;
- Published and widely distributed guidance on: the decontamination of endoscopes; benchtop sterilisers; latex glove sensitisation; safe use of lasers; wheelchair and vehicle passenger lifts; the processing, storage and issue of bone marrow and blood stem cells; and the electromagnetic compatibility of medical devices with mobile communication equipment;
- Held three Study Days for NHS nurses, risk managers and biomedical engineers, to describe the Agency's work and the part attendees play in using medical devices safely.
- Contributed to the work of some 140 Committees and Working Groups writing new European and international safety standards, chairing 10 British Standards Institution committees and convening 18 international Working Groups.
- Negotiated for the UK at 16 meetings on the European Commission's proposal for a Directive covering In Vitro diagnostic medical devices.
- Reported 22 incidents to the European Commission and other Member States under the vigilance system required by the Directives for medical devices, all within our customer service target of five days; we received 13 in return;
- Reviewed 55 proposals for the UK clinical investigation of pre-market medical products with an average turnaround time of 46 days and all within 60 days.
- Made 140 presentations on the UK Medical Devices Regulations and device safety at national and international conferences and seminars.
- Developed an enforcement strategy for the UK Regulations and trained staff in its operation.
- Played an influential role in six Working Groups defining interpretation and implementation details of the European Directives and UK Regulations; and to four international Study Groups discussing global harmonisation issues;
- Published 143 device evaluation reports to the NHS, two Diagnostic Imaging Reviews and 14 reports on products for disabled people;
- Improved operational efficiency by 10%;

- Held running costs 18.2% below budget while maintaining services;
- Contributed to 54 answers to Parliamentary Questions and Private Office cases and provided advice to Ministers, the Department of Health and other Government Departments, all in time to meet the required deadlines.
- Provided 384 answers in writing to enquiries concerning the Medical Devices Regulations, and responded to 2990 requests for information packs, achieving virtually 100% Code of Practice levels of services in both cases.
- Maintained the Manufacturer Registration Scheme Register and prepared for its orderly cessation during 1998; and
- Completed two surveys of hospital staff to investigate whether Device Evaluation Reports meet customer needs and started one of General Practitioners

Appendix XXI

Declaration of Interests by the Members of the Medicines Commission and Committee on Safety of Medicines (1997)

Table A Declaration of Interests by the Members of the Medicines Commission (1997)[1]

Professor D.H. Lawson (Chairman)	None
Professor S. Campbell	None
Professor S.S. Davis	*Personal:* Danbiosyst (UK) Ltd [Shares, salary]; Pharmaceutical Profiles [Shares, salary]; Eli Lilly (USA)[Consultancy]; Nycomed (Imaging)[Consultancy]; Hoechst (UK)[Consultancy]; GeneMedicine (USA)[Fees, stock options]; Aradigm [Fees, stock options]; Piere Fabre (France)[Consultancy]; and 3M Healthcare (UK) [Consultancy]. *Non-Personal:* SmithKline Beecham; Pfizer [Research Grant]; Zeneca; and Glaxo Wellcome [Research Grant].
Professor A.D. Dayan	*Personal:* SmithKline Beecham; Organon International; Amgen; Cantab Ltd; Roche; Novartis; Alkermes; Daichii; Amylin; and Janssen [Consultancies]. *Non-Personal:* Otsuka Pharmaceuticals [Research].
Professor E. Ernst	*Personal:* Boots [Donation]; Merck Sharp Dohme [Donation]; Lichtwer [Donation]; Bio Diet London [Fees]; and Bionorica Germany [Fees]
Professor R. Jones	*Personal:* SmithKline Beecham; Zeneca; and Glaxo Wellcome [Shares]
Dr P. Kumar	*Non-Personal:* Roche; and Schering-Plough [Funding for a Hepatitis Registrar].
Miss A. Lewis	*Non-Personal:* La Gap Pharmaceuticals [Contribution].
Dr C. McCartney	None.
Dr A. McKnight	None.
Mr D. Miller	*Personal:* Novartis [Salary].
Dr C. Newdick	*Personal:* Astra [Fees]; Glaxo Wellcome [Fees]; and 3M Healthcare [Fees].

[1] Medicines Commission et al (1997) pp78-80.

Table A contd.

Professor J. Newton	*Personal:* Norgine [Consultancy]; Glatt GmbH [Consultancy]; Bosch [Consultancy]; Takeda [Consultancy]; SmithKline Beecham [Consultancy]; Capsugel [Consultancy/Grants]; and Rhone-Poulenc Rorer [Consultancy/Grants]. *Non-Personal:* Glaxo Wellcome; Rhone-Poulenc Rorer; Glatt GmbH; FMC; Sankyo Ltd; and BTG [Research Grants].
Professor S. Pocock	*Personal:* Merck [Fees]; Astra Hasole [Fees]; Astra Arcos [Fees]; Genetech [Fees]; Bayer [Fees]; SmithKline Beecham [Consultancy]; and Eisai [Consultancy] Non-Personal: Roche; and Astra Draco [Grants].
Dr A.G. Renwick	*Personal:* International Sweeteners Association [Consultancy]. *Non Personal:* SmithKline Beecham; Pfizer; and Unilever [Research support].
Mrs J. Shott	*Personal:* Proctor & Gamble [Salary, shares]
Dr. D. Williams	None
Mr H. C. Wilson	None

Table B Declaration of Interests by the Members of the Committee on Safety of Medicines (1997)[2]

Professor M.D. Rawlins (Chairman)	None
Professor T.R.E. Barnes	*Personal:* Eli Lilly [Consultancy]; Knoll Pharmaceuticals [Consultancy]; Ortho McNeil [Consultancy]; Sandoz [Consultancy]; Worldwide Clinical Trials [Consultancy]; Zeneca [Consultancy]; and Lundbeck [Sponsorship for meetings]. *Non-Personal:* Eli Lilly [Research Grant].
Professor A.M. Breckenridge	*Personal:* SmithKline Beecham [Member of Scientific Advisory Committee]. *Non Personal:* Glaxo Wellcome; Organon Labs Ltd; Parke Davis Research Labs; Pfizer Ltd; Sandoz Pharmaceuticals; Schering Health Care Ltd; Zeneca [Research Grants]
Dr K.L. Costeloe	*Non-Personal:* Serono Labs (UK) Ltd [Research Grant]

[2]Ibid pp81-90.

Table B contd.

Dr J.H. Darbyshire	*Personal:* Genomyc; and Phairson [Board Member]. *Non-Personal:* Bristol-Myers Squibb, Glaxo Wellcome, Janssen, Roche and SKB [Support for Clinical Trials].
Professor H.J. Dargie	*Personal:* Lilly; MSD, Rhone-Poulenc Rorer; Roche; and SmithKline Beecham [Consultancies]. *Non-Personal:* Bayer [Clinical Trials Funding]; Bristol-Myers Squibb [Clinical Trials Funding]; E. Merck [Clinical Trial]; MSD [Diagnostic Study]; Pfizer [Clinical Trial]; and SKB [Clinical Trial].
Professor D.S. Davies	*Personal:* ICI [Shareholder]; Zeneca [Shareholder]; ML Laboratories [Non-Executive Director and Shareholder]; and Schering-Plough USA [Consultancy]. *Non Personal:* Astra/Draco; Boehringer Mannheim; Bristol Myers Squibb; Genentech; Glaxo Wellcome; Hoechst; Janssen; Kali-Chemi Pharma; Knoll Pharmaceuticals; Lilly Research; ML Laboratories; MSD; Orion-Farmos; Parke-Davis; Pharmacia/Upjohn; Pfizer; Prodesfarma; Rhône-Poulenc Rorer; Roche; Sanofi Winthrop; Schwarz Pharma; Servier; SmithKline Beecham; Solway Health Care; [Commissioned Research, Fellowships, Grants, Consultancy and Meeting Support]. Upjohn (Research) and Zeneca [Research, Grants and Fellowships] TAP Holdings [Royalties] Astra AB; Bayer plc; Bochringer Ingelheim; British Biotech; Ciba-Geigy Ltd; Glaxo Wellcome R&D; Hoechst Marion Roussel; Hoffman-La Roche; Janssen Research Fund; MSD; ML Labs plc; Schering AG; Schering -Plough Research; Institut de Recherches; SKB R&D; Synthelabo Recherche (LERS); Upjohn Laboratories; and Zeneca Pharmaceuticals [Financial Contribution to Scientific Meeting]
Dr A.M. Douglas	None
Professor G.W. Duff	*Personal:* Medical Science Systems [Stockholder]; SKB [Consultancy]; and Zeneca [Advisory Board Member]. *Non-Personal;* Amgen [Contract Work]; Glaxo Wellcome [Studentship]; and Pfizer [Academic Collaboration].
Dr S.J. Eykyn	None
Professor R.G. Finch	*Personal:* Bristol Myers Squibb; Glaxo Wellcome; Hoechst Marion Roussel; Nexstar; Rhône-Poulenc Rorer; SKB; Upjohn; Wyeth Lederle; and Zeneca [Consultancies]

Table B contd.

Professor A.T. Florence	*Personal:* Napp Research [Consultancy]; Baker-Norton [Research Grant]; Lipha [Research Grant]; and Sandoz (Novertis) [Research Grant]. *Non Personal:* Access Pharmaceuticals; Alchemia Pty Ltd; Ares-Serono; Astra Pain Control AB; Astra Pharmaceuticals Ltd; Bristol Myers Squibb; Capsugel AG; Cortecs International Ltd; Dow Chemical; FMC Corporation; Glatt GmbH; Glaxo Wellcome, Glaxo Wellcome Italy; ICI Surfactants; Kelco; Lilly Industries Ltd; L'Oreal; Medell Inc; ML Laboratories plc; Nearmedic Ltd; Norgine; Norton Healthcare Ltd; Pfizer Ltd; Reckitt & Coleman Products; Rhône-Poulenc Rorer; Roche Products Ltd; Sanofi Winthrop; Shell International; SmithKline Beecham; Transgene S.A., Unilever Research; Wellcome Research; Wyeth Manufacturing (UK); and Zeneca Pharmaceuticals [Research Grants for School of Pharmacy of which Professor Florence is Dean].
Professor E.C. Gordon-Smith	*Non-Personal:* Amgen [Research Grant]; Chugai Pharma UK Ltd [Research Grant]; Merieux UK Ltd [Travel Grant]; Roche Products Ltd [Research Grant]; and Sandoz Pharmaceuticals [Research Grant].
Professor K. Gull	*Personal:* Athena Neurosciences [Consultancy]; Kent Life Sciences [Salary]; and RBM (Italy) [Consultancy]. *Non-Personal:* Advanced Technologies; Astra Hassle; Celltech; Glaxo Wellcome; Hoechst; Johnson & Johnson; Knoll Pharma; Novo Nordisk; Pfizer; Roche; Scotia; SKB; Unilever; Yamanouchi; and Zeneca [Research for School of Biological Sciences, University of Manchester].
Professor H.S. Jacobs	*Personal:* Glaxo Wellcome [Shareholder]; and Sandoz [Co-defendants in a legal case] *Non Personal:* Ferring [Travel Grants]; Ipsen [Grants]; Organon [Fees]; and Pharmacia/Upjohn [Grants].
Mrs E.A. Kay	None
Dr M.J. Kendall	*Personal:* Astra Hassle [Advice and Lectures]. *Non-Personal:* Astra Germany; Fournier; MSD; and Sanofi Winthrop [Departmental Research].
Dr B.J. Kirby	*Non-Personal:* Bayer plc [Consultancy Fee].
Dr S. Kumar	None

Table B contd.

Professor M.J.S. Langman	*Personal:* Knoll Pharmaceuticals [Consultancy]; and MSD [Fees]. *Non Personal:* Astra Pharmaceuticals [Surveillance Study]; Bayer [Consultancy]; Roche [Surveillance Study]; Bayer UK; Bochringer Ingelheim; Boots; British Biotech; Ciba Pharmaceuticals; FDM; Fisons plc; Glaxo Research & Development; Hoechst Roussel Ltd; ICI; Janssen; Johnson & Johnson; Medac; Novo Nordisk; Organon Laboratories; Pfizer; Pharmacia; Proctor & Gamble; Roche Products; Rhône-Poulenc Rorer; Sandoz (UK); Sanofi Winthrop; SmithKline Beecham; and Zeneca [Support for Department of Medicine Research Activities of which Professor Langman is head.].
Dr A.V.P. Mackay	*Personal:* Lilly Industries Ltd [Consultancy/Fees] *Non-Personal:* Scotia Pharmaceuticals Ltd [Research Grant Support]
Professor J.M. Midgley	*Personal:* Amylin (Europe) [Consultancy]; Mitsubishi Chemical (UK) [Consultancy]; Oxford Glycosciences [Consultancy]; and Phairson Medical Ltd [Consultancy]. *Non Personal:* Glaxo Wellcome [Research Support]
Professor B.K. Park	*Non Personal:* Boots; Glaxo; Parke-Davis; Pfizer; and Roche [PhD Studentships and Research Fellowships]
Professor J.C. Petrie	*Non-Personal:* Bayer UK Ltd; Bochringer Ingelheim Ltd; Bristol-Meyers Squibb; Glaxo; Lilly; E. Merck; Pfizer; Pharmacia; Rhône-Poulenc Rorer; Roche; Schering Plough; Servier; SmithKline Beecham; E.R. Squibb; Wellcome Trust; Wyeth; and Zeneca [Support towards Student Fellowships for MSc course. Research grants & Clinical Trials].
Professor L.L. Smith	*Personal:* Rhône-Poulenc [Consultancy]; Wyeth Ayerst Research [Consultancy]; and Zeneca plc [Shareholder]. *Non-Personal:* Astra plc; Orion plc; Pfizer; Rhône-Poulenc Rorer; and Zeneca plc [Grants to Toxicology Unit].
Dr K. Verrier Jones	*Personal:* Dalgety plc; Hanson plc; ICI; The Energy Group plc; US Industries Inc; Zeneca; and Millenium Chemicals [Shares]. *Non-Personal:* Beecham [Talk on Antibiotic Policy]; Bochringer Ingelheim [Patient Information Booklet]; and Sandoz [Studies on Neoral AUC in children].

Table B contd.

Professor M.P. Vessey	*Personal:* Novo-Nordisk Pharms; Proctor & Gamble Pharms; and Lilly Research Labs [Consultancies]. *Non-Personal:* Abbott Labs Ltd; Astra Pharmaceuticals Ltd; Bayer plc; Fresenius AG; Janssen-Cilag; Lilly Industries; Merck Sharp & Dohme Ltd; Panpharma Ltd; Parke Davis & Co; Rhône-Poulenc Rorer; and Wyeth [Research Grants, Consultancies and/or Research Advice].
Professor I.V.D. Weller	*Personal:* Bristol Myers Squibb [Honorarium]. *Non-Personal:* Boehringer; British Biotech; Gilead Sciences; Glaxo Wellcome; SKB; and 3M Healthcare.

Appendix XXII

Medicinal Products which have been transferred from Prescription Only to Pharmacy status (1983 - 1997)[787]

[787]S.I. 1984/756, 1986/586, 1987/674, 1987/1250, 1988/2017, 1989/1852, 1991/962, 1992/1534, 1994/3016 and 1995/1384.

Active Substance [Enabling Statutory Instrument] Date in force	Limitations
Ibuprofen [S.I. No. 1983/1212 and 1987/674] ?1983 and 30 April 1987	Sustained release formulations and ordinary oral preparations with a maximum dose of 400 mg
Hydrocortisone [S.I. No. 1987/674] 30 April 1987	Topical preparations
Mebendazole [S.I. No. 1989/1852, amended by 1993/3256 and 1996/3193] 1 November 1989 and 21 January 1994	(a) the medicinal product is indicated for oral use in the treatment of enterobiasis in adults and in children over the age of 2 years; (b) its container or package is labelled to show a maximum dose of 100 milligrams of mebendazole; and (c) it is sold or supplied in a container or package containing not more than 800 milligrams of mebendazole.
Hyoscine Butylbromide [S.I. No. 1991/962] 1 May 1991	(a) its route of administration is internal otherwise than by inhaler; (b) it is sold or supplied in a container or package containing not more than 240mg; and (c) its container or package is labelled to show a maximum daily dose of 80mg and a maximum dose of 20mg.
Carbenoxolone sodium [S.I. No. 1992/2937] 18 December 1992	(a) the medicinal product is in the form of granules; (b) the maximum strength of the carbenoxolone sodium in the medicinal product does not exceed one per cent calculated in terms of weight in weight; (c) the medicinal product is sold or supplied in a container or package containing not more than 560 milligrams of carbenoxolone sodium; (d) the container or package of the medicinal product is labelled to show a maximum daily dose of 80 milligrams of carbenoxolone sodium and a maximum dose of 20 milligrams of carbenoxolone sodium; and (e) the medicinal product is indicated only for treatment, by mouthwash, in adults and in children over the age of 12 years.

Active Substance [Enabling Statutory Instrument] Date in force	Limitations
Acrivastine [S.I. No. 1993/1890] 23 August 1993	(a) the medicinal product is sold or supplied in a container or package containing not more than 240 milligrams of acrivastine; (b) its container or package is labelled to show a maximum daily dose of 24 milligrams of acrivastine.
Cetrizine Hydrochloride [S.I. No. 1993/1890] 23 August 1993	(a) the medicinal product is sold or supplied in a container or package containing not more than 100 milligrams of cetrizine; and (b) its container or package is labelled to show a maximum daily dose of 10 milligrams of cetrizine.
Ketoprofen [S.I. No. 1993/1890] 23 August 1993	(a) the maximum strength of the ketoprofen in the medicinal product does not exceed two point five per cent calculated in terms of weight in weight; (b) the medicinal product is sold or supplied in a container or package containing not more than 30 grams of the medicinal product; (c) the medicinal product is indicated only for treatment by external topical application, for rheumatic and muscular pain, in adults and in children over the age of 12 years, for a maximum period of 7 days.
Loratadine [S.I. No. 1993/1890] 23 August 1993	(a) the medicinal product is sold or supplied in a container or package containing not more than 100 milligrams of loratadine; and (b) its container or package is labelled to show a maximum daily dose of 10 milligrams of loratadine.
Terfenadine [S.I. No. 1993/1890] 23 August 1993	(a) the medicinal product is sold or supplied in a container or package containing not more than 1200 milligrams of terfenadine; (b) its container or package is labelled to show a maximum daily dose of 120 milligrams of terfenadine.
Beclomethasone dipropionate [S.I. No. 1993/3256] 21 January 1994	(a) the medicinal product is indicated only for the treatment of seasonal allergic rhinitis by non-aerosol nasal administration, in adults and in children over the age of 12 years; (b) it is sold or supplied in a container or package containing not more than 200 doses; (c) its container or package is labelled to show a maximum dose of 100 micrograms per nostril and a maximum daily dose of 200 micrograms per nostril of beclomethasone dipropionate.

Active Substance [Enabling Statutory Instrument] Date in force	Limitations
Cimetidine [S.I. No. 1993/3256] 21 January 1994	(a) the medicinal product is indicated for the short-term symptomatic relief of heartburn, dyspepsia and hyperacidity; and (b) its container or package is labelled to show a maximum dose of 100 milligrams of cimetidine to be taken once daily at night
Cimetidine [S.I. No. 1993/3256] 21 January 1994	(a) the medicinal product is for the prophylactic management of nocturnal heartburn; and (b) its container or package is labelled to show a maximum dose of 100 milligrammes of cimetidine to be taken once daily at night for a maximum period of 14 days.
Famotidine [S.I. No. 1993/3256, as amended by 1996/3193] 21 January 1994	(a) (i) the medicinal product is indicated for the short-term symptomatic relief of heartburn, dyspepsia, indigestion, acid indigestion or hyperacidity; and (ii) the prevention of the symptoms of heartburn, dyspepsia, indigestion, acid indigestion or hyperacidity where they are associated with the consumption of food or drink, including the prevention of sleep disturbance due to those symptoms and (b) its container or package is labelled to show a maximum dose of 10 milligrams and a maximum daily dose of 20 milligrams of famotidine for a maximum period of 14 days.
Sodium Cromoglycate (drops) [S.I. No. 1993/3256] 21 January 1994	(a) the medicinal product is indicated for the treatment of acute seasonal allergic conjunctivitis; (b) it is in the form of aqueous eye drops; (c) the maximum strength of the sodium cromoglycate in the medicinal product does not exceed two per cent calculated in terms of weight in volume; and (d) it is sold or supplied in a container containing not more than 10 millilitres of the medicinal product.
Sodium cromoglycate (ointment) [S.I. No. 1993/3256] 21 January 1994	(a) the medicinal product is indicated for the treatment of acute seasonal allergic conjunctivitis; (b) it is in the form of an eye ointment; (c) the maximum strength of the sodium cromoglycate in the medicinal product is four per cent calculated in terms of weight in weight; (d) it is sold or supplied in a container or package containing not more than 5 grams of the medicinal product.

Active Substance [Enabling Statutory Instrument] Date in force	Limitations
Diclofenac diethylammonium [S.I. 1994/3016] 30 December 1994	(a) the maximum strength of the diclofenac diethyl ammonium in the medicinal product does not exceed 1.16 per cent calculated in terms of weight in weight; (b) the medicinal product is indicated for external application for the local symptomatic relief of pain and inflammation in trauma of the tendons, ligaments, muscles and joints and in localised forms of soft tissue rheumatism, in adults and in children of not less than the age of 12 years; (c) it is sold or supplied in a container or package containing not more than 30 grams of the medicinal product; and (d) its container or package is labelled to show a maximum period of use of 7 days.
Felbinac [S.I. No. 1994/3016] 30 December 1994	(a) the maximum strength of the felbinac in the medicinal product does not exceed 3.17 per cent, calculated in terms of weight in weight. (b) the medicinal product is indicated for external application for the relief of symptoms associated with soft tissue injury such as strains, sprains and contusions, in adults and in children of not less than the age of 12 years; (c) it is sold or supplied in a container or package containing not more than 30 grams of the medicinal product; and (d) the container or package is labelled to show a maximum period of use of 7 days.
Flunisolide [S.I. No. 1994/3016] 30 December 1994	(a) the medicinal product is in the form of a non-pressurised nasal spray; (b) the maximum strength of the flunisolide in the medicinal product does not exceed 0.025 per cent calculated in terms of weight in volume; (c) the medicinal product is indicated for the prevention and treatment of seasonal allergic rhinitis, including hayfever, in adults and in children of not less than the age of 12 years; (d) it is sold or supplied in a container or package containing not more than 240 metered doses of the medicinal product; and (e) the container or package is labelled to show a maximum dose of 50 micrograms per nostril and a maximum daily dose of 100 micrograms per nostril of flunisolide in the case of adults and children over the age of 16 years and a maximum dose of 25 micrograms per nostril in the case of other children of not less than the age of 12 years.

Active Substance [Enabling Statutory Instrument] Date in force	Limitations
Oxethazaine [S.I. No. 1994/3016] 30 December 1994	(a) it is sold or supplied in a container or package containing not more than 400 milligrams of oxethazaine; and (b) its container or package is labelled to show a maximum dose of 10 milligrams and a maximum daily dose of 30 milligrams of oxethazaine.
Piroxicam [S.I. No. 1994/3016] 30 December 1994	(a) the maximum strength of the piroxicam in the medicinal product does not exceed 0.5 per cent calculated in terms of weight in weight; (b) the medicinal product is indicated for external application for the relief of rheumatic pain and muscular aches, pains and swellings such as strains, sprains and sports injuries, in adults and in children of not less than the age of 12 years; (c) it is sold or supplied in a container or package containing not more than 30 grams of the medicinal product; and (d) its container or package is labelled to show e maximum period(of use of 7 days.
Ranitidine hydrochloride [S.I. No. 1994/3016] 30 December 1994	(a) the medicinal product is indicated for the short term symptomatic relief of heartburn, dyspepsia and hyperacidity; (b) its container or package is labelled to show a maximum dose equivalent to 75 milligrams of ranitidine and a maximum daily dose equivalent to 300 milligrams of ranitidine for a maximum period of use of 14 days.
Fluconazole S.I. No. 1995/1384 30 June 1995	(a) the medicinal product is indicated for oral administration for the treatment of vaginal candidiasis in persons aged not less than 16 years nor more than 60 years; (b) it is sold or supplied in a container or package containing not more than 150 milligrams of the medicinal product: and (c) the container or package is labelled to show a maximum dose of 150 milligrams of fluconazole.
Hydroxyzine hydrochloride S.I. No. 1995/1384 30 June 1995	(a) the medicinal product is indicated for the management of pruritus associated with acute or chronic urticaria or atopic dermatitis or contact dermatitis, in adults and in children aged not less than 6 years; (b) it is sold or supplied in a container or package containing not more than 750 milligrams of the medicinal product; and (c) the container or package is labelled to show a maximum dose of 25 milligrams and a maximum daily dose of 75 milligrams in the case of adults and in children aged not less than 12 years and a maximum daily dose of 50 milligrams in the case of children aged not less than 6 nor more than 12

	years.
Active Substance [Enabling Statutory Instrument] Date in force	**Limitations**
Ketoconazole S.I. No. 1995/1384 30 June 1995	(a) the medicinal product is in the form of a shampoo; (b) the maximum strength of the ketoconazole in the medicinal product does not exceed 2 per cent calculated in terms of weight in weight; (c) the medicinal product is indicated for the prevention and treatment of dandruff and seborrhoeic dermatitis of the scalp; (d) it is sold or supplied in a container or package containing not more than 120 millilitres of the medicinal product, containing not more than 2400 milligrams of ketoconazole; and (e) the container or package is labelled to show a maximum frequency of application of once every three days.
Pyrantel embonate S.I. No. 1995/1384 30 June 1995	(a) the medicinal product is indicated for the treatment of enterobiasis, in adults and in children aged not less than 2 years; (b) it is sold or supplied in a container or package containing not more than 750 milligrams of the medicinal product; and (c) the container or package is labelled to show a maximum daily dose (to be taken as a single dose) of pyrantel embonate of 750 milligrams in the case of adults and children aged not less than 12 years, of 500 milligrams in the case of children aged not less than 6 nor more than 12 years and of 250 milligrams in the case of children aged not less than 2 nor more than 6 years.
Budesonide [S.I. No. 1995/3174] 29 December 1995	(a) the medicinal product is indicated only for the prevention or treatment of seasonal allergic rhinitis in adults and in children aged not less than 12 years; (b) it is in non-aerosol, aqueous form for nasal administration; (c) it is sold or supplied in a container or package containing not more than 10 milligrams of the medicinal product; and (d) the container or the package is labelled to show a maximum dose, and a maximum daily dose, of 200 micrograms per nostril of budesonide.

Active Substance [Enabling Statutory Instrument] Date in force	Limitations
Azelastine hydrochloride [S.I. No. 1996/1514] 5 July 1996	(a) the medicinal product is indicated only for the treatment of seasonal allergic rhinitis in adults and in children aged not less than 12 years; (b) it is in non-aerosol, aqueous form for nasal administration; (c) it is sold or supplied in a container or package containing not more than 36 doses, each of which contains not more than 140 micrograms of azelastine hydrochloride; and (d) the container or package is labelled to show a maximum dose of 140 micrograms per nostril of azelastine hydrochloride and a maximum daily dose of 280 micrograms per nostril of azelastine hydrochloride.
Nizatidine [S.I. No. 1996/1514] 5 July 1996	(a) the medicinal product is indicated only for the prevention of the symptoms of food-related heartburn in persons aged not less than 16 years; and (b) the container or package is labelled to show a maximum dose of 75 milligrams of nizatidine and a maximum of 4 such doses in any period of 14 days.

Appendix XXIII

Unsupervised Sales of Pharmacy Medicines reported to the Statutory Committee (1986 - 1997)[288]

[288]Based on case reports published in the Pharmaceutical Journal.

1986		
Alun Gwnfor Cunnah [Pharm J, 1 March 1986, p270]	Mold Magistrates Court 26 March 1985 Four supply offences Fined £100; Costs £75	No action [23 January 1986]
Petter Pharmacies Limited [Pharm J, 26 April 1986, p533]	Tottenham Magistrates Court 24 June 1985 One offence Fined £200	Admonition [27 February 1986]
Dilip Gordonbhai Patel and Blendcross Limited [Pharm J, 10 May 1986]	Greenwich Magistrates Court Date not specified Two sale and three supply offences Company fined £5000; Costs £200 Pharmacist fined £1250 (29 other offences were taken into consideration)	Both reprimanded [18 March 1986]
A.K.C. Patel and Mearnhurst Limited [Pharm J, 27 July 1985, p129 and 12 July 1986, p58]	Court not specified 26 November 1984 Two sale offences Company fined £200; Costs £250	Both reprimanded [10 June 1986, adjourned from 25 June 1985]
M.E. Malkiewicz [Pharm J, 18 October 1986, p493]	Court not specified 5 February 1985 Two sale offences Two year conditional discharge	Reprimand [10 September 1986, adjourned from 26 September 1985]
1987		
Satish Kumar Jalota and Hill Top Pharmacy Limited [Pharm J, 31 May 1986 p710 and 27 June 1987, p797]	Smethwick Magistrates Court 2 October 1985 Two sale offences Both fined £600	Pharmacist and company disqualified. [7 April 1987]
John Bernard McLafferty [Pharm J, 27 June 1987 p797]	Glasgow Sheriff Court 17 September 1986 One offence Sentence not specified	Reprimand [6 May 1987]
Satyandraprasad Jashbhai Patel [Pharm J, 5 September 1987, p272]	Caerphilly Magistrates Court 25 August 1986 (?) Two offences Fined £1000; Costs £200 (Four other offences were taken into consideration)	Reprimand [date unspecified]

Donald Illingworth (superintendent pharmacist) and J. Robertson & Son Limited [Pharm J, 17 October 1987]	Court not specified Two offences Company fined £200; Costs £40 Pharmacist fined £50; Costs £40	Both reprimanded [27 August 1987]
Zulfkar Ahmed Akram [Pharm J, 28 November 1987, p670]	Barnsley Magistrates Court 22 January 1987 (?) One offence Fined £200; Costs £50 (Fine also covered one labelling offence)	Admonishment [1 October 1987]
1988		
Suresh Vaghjibhai Madhardas Patel and Savegreen Ltd [Pharm J, 27 February 1988, p289]	No prosecution mentioned	Not guilty [16 November 1987]
Brian Ashworth [Pharm J, 28 May 1988, p704]	Warley Magistrates Court 23 June 1987 Two offences Fined £200; Costs £50	Reprimand [18 January 1988]
Hywel Thomas Davies and Hywel Davies Limited [Pharm J, 9 July 1988, p52]	Caerphilly Magistrates Court 15 December 1987 Two offences Company fined £500; Costs £200	Reprimand for company and pharmacist. [24 March 1988]
Peter Hywel Lewis [Pharm J, 9 July 1988, p53]	Carmarthen South Magistrates Court 16 September 1987 One offence Fined £100; Costs £200	Reprimand [24 March 1988]
Jayeshkumar Vithalbhai Patel (superintendent pharmacist) and Alpine Pharmacy Limited (no longer trading) [Pharm J, 27 August 1988, p280]	Croydon Magistrates Court 8 September 1987 Four offences Company fined £2000; Costs £250 (27 similar offences were taken into consideration)	Pharmacist was admonished; No action was taken against the company as it was no longer trading. [14 July 1988]
Rakesh Kumar Panesar [Pharm J, 22 October 1988, p548]	Oldbury Magistrates Court 16 February 1988 One offence Fined £250; Costs £75	Reprimand [7 September 1988]
Jitendrakumar Manubhai Desai [Pharm J, 22 October 1988, p548]	Birmingham Magistrates Court 24 August 1987 One offence Fined £100; Costs £100	Reprimand [8 September 1988]
Yakub Ismail Patel [Pharm J, 22 October 1988, p549]	20 October 1986 Two offences Fined	Reprimand

Rajinder Tanday [Pharm J, 26 November 1988, p697]	Medway Magistrates Court 2 March 1988 One offence Fined £500; Costs £25	Reprimand
1989		
Healthwise Limited [Pharm J, 18 March 1989, p321]	Bolton Magistrates Court 25 March 1988 Three offences Fined £600; Costs £25	Striking-off order [14 December 1988]
Paul Michael Glaser (superintendent pharmacist) [Pharm J 19 August 1989, p230]	Windsor Magistrates Court 9 June 1988 Four offences Company and non-pharmacist director fined £2000 each; costs £125	No action [19 April 1989]
Salil Kumar Gupta [Pharm J, 21 October 1989, p526]	Woolwich Magistrates Court 18 October 1988 Two offences Fined £500; Costs £100	Reprimand [26 September 1989]
Manmohan Singh Birk and Harbhajan Singh Nagra [Pharm J, 21 October 1989, p526]	Warwick Magistrates Court 4 October 1988 Two offences Fined £200 each	Admonition
1990		
John Denis Burridge [Pharm J, 30 June 1990, p803]	Swansea Magistrates' Court 24 August 1989 One offence Fined £200; Costs £200	Reprimand [11 April 1990]
Bhimji Kalyan Virji Patel and Patels Chemists Limited [Pharm J, 4 August 1990, p158]	Oldham Magistrates' Court 17 November 1988 One offence Pharmacist fined £100 Company fined £200 Costs: £50	Reprimand [9 May 1990]
Stuart Clark Cunningham [Pharm J, 18 August 1990]	Sheriff Court of Glasgow and Strathkelvin 4 July 1989 One offence Admonished	Reprimand [22 June 1990]

Paul Norman Cohen [Pharm J, 22 September 1990, p406]	Not charged with any criminal offence, but he was the superintendent pharmacist and the company and director had been found guilty of criminal offences.	Reprimand [19 July 1990]
1991		
Mehboob Fatehalli Vaiya [Pharm J, 12 January 1991, p54]	Leicester Magistrates' Court 25 October 1990 Two offences Fined £250; Costs £180	Reprimand [25 October 1990]
Jitendrakumar Katechia [Pharm J, 19 January 1991 p89]	Gray's Magistrates' Court 24 October 1990 One offence Fined £500; Costs £50	Reprimand [24 October 1990]
Opalrise Limited [Pharm J, 16 March 1991, 340]	Long Sutton's Magistrates' Court 18 January 1990 One offence Fined £150; Costs £175	Disqualified [19 December 1990] Pharmacist director found guilty of forgery and later died
Calstar Limited [Pharm J, 27 July 1991, p136]	Birmingham Magistrates' Court 12 October 1990 One offence Fined £250; Costs £75	Reprimand [19 June 1991]
Mohamed Gulamabbas Fazal [Pharm J, 17 August 1991, p224]	Birmingham Magaistrates' Court 20 March 1990 One offence Two year conditional discharge	Reprimand [19 June 1991]
Gillian Katherin Hughes [Pharm J, 17 August 1991, p225]	Pontypridd Magistrates' Court 18 October 1990 Several offences Sentence not specified	Admonished [20 June 1991]
UG's Pharmacies Limited and Arun Narbheram Nandha (superintendent pharmacist) [Pharm J, 1 February 1992, p150]	Marylebone Magistrates Court 1 March 1991 Two charges Company fined £400; Costs £200	Company received a reprimand; Pharmacist, who was on holiday at the time of the offences, was found not guilty. [18 December 1991]

1992		
Virendra Narendra Dahyabhai Patel (director and superintendent pharmacist) and Cristal Limited [Pharm J, 30 May, 1992 p712]	Greenwich Magistrates Court 18 April 1991 Two offences Company fined £300; Costs £250	No action taken because of technical reasons (company no longer existed). [18 March 1992]
Aruna Jayantilal Patel [Pharm J, 13 June 1992, p777]	Ealing Magistrates Court 3 May 1991 One offence Sentence unspecified	Reprimand [14 April 1992]
Beebee Aziza Bundhoo [Pharm J, 13 June 1992, p777]	Highbury Corner Magistrates Court 17 July 1991 One offence Fined £150; Costs £250	Admonition [14 April 1992]
Punil Thakrar [Pharm J, 27 June 1992, p841]	South Western Magistrates Court 23 October 1991 One offence Fined £150; Costs £50	Reprimand [26 May 1992]
1993		
Kantilal Dahyabhai Nathoo Mistry [Pharm J, 26 June 1993, p868]	Brent Magistrates Court 2 April 1992 One offence Fined £300; Costs £1000 [Fine also covered one supervision offence]	Reprimand [20 April 1993]
Laura Wendy Barlow [Pharm J, 31 July, p162]	No details of any prosecution.	Reprimand [22 June 1993] Also, misconduct included smoking and keeping dogs in the dispensary.
Johnathan Ralph Feast (superintendent pharmacist) and Ransley Robinson Chemists Limited [Pharm J, 11 December 1993, p806]	Worthing Magistrates' Court 28 May 1992 One offence Company fined £500; Costs £500	Company reprimanded. No action taken against superintendent pharmacist) [22 July 1993]
Anil Paul Khanna and Sunil Paul Khanna [29 January 1994, p154]	Newcastle upon Tyne Magistrates' Court Two offences Fined £400; Costs £1000	Reprimand [21 April and 28 September]

1994		
Nasreen Kausar Ali [Pharm J, 25 June 1994, p891]	Swansea Magistrates Court 26 May 1993 One offence Fined £1410; Costs £800	Reprimand [15 March 1994]
Richard Scott Cole and David John Williams (Directors and shareholders of Cromabrook Limited) [3 September 1994, p308]	Mid-Glamorgan Magistrates' Court 17 March 1993 One offence Cole fined £750 Company fined £750; Costs £759	Reprimand [1994]
Jayprakash Shantilal Patel [Pharm J, 8 October 1994, p496]	Wells Street Magistrates Court 8 July 1993 One offence Fined £500; Costs £1000	Reprimand [20 July 1994]
Errol Gordon Dulipsinji Ganpatsingh [Pharm J, 19 November 1994, p719]	Brighton Magistrates Court 15 July 1994 Two offences Fined £2,000; Costs £1,476	Reprimand [16 August 1994]
Bhupinder Singh Bharj [Pharm J, 26 November 1994, p752]	Leeds Magistrates Court 24 February 1994 One offence Fined £250; Costs £442.50	Striking-off order [27 September 1994; the case also involved the sale of out-of-date medicines, the re-use of patient-returned medicines and the substitution of medicines.]
Tirfe Beyene [Pharm J, 18 February 1995, p221]	South Western Magistrates Court 25 October 1993 Two offences Fined £400; Costs £1,138	Reprimand [15 November 1994]
Sanjay Chopra [Pharm J, 18 February 1995, p221]	Leighton Buzzard Magistrates Court 17 November 1993 One offence Fined £350; Costs £100	Reprimand [17 November 1994]
Najamalhussein Mohamedali Rajabali Khimji (superintendent pharmacist) [Pharm J, 25 February 1995, p255]	Wells Street Magistrates Court 29 October 1993 Two offences Fined £300	Reprimand [14 December 1994]

1995		
Manjeet Singh [Pharm J, 19 August 1995, p246]	Brighton and Hove Magistrates' Court 10 August 1994 One offence Fined £500; Costs £893.99	Reprimand [16 May 1995]
Sidney Maxwell Hutchison (superintendent pharmacist) and S.M. Hutchison (Chemist) Ltd [Pharm J, 17 February 1996]	Tower Bridge Magistrates' Court 15 March 1995 Five offences 12 month Conditional Discharge; Costs: £250 Company fined £1,250; Costs: £500	Striking-off order [21 September 1995]
1996		
James Lee McCrindle [Pharm J, 1 February 1997]	No prosecution	Reprimand [16 October 1996] Also involved, no protocol for the sale of medicines.
Wai Man Yong [Pharm J, 1 February 1997	Newcastle upon Tyne's Magistrates'Court Two offences Fined £3000; Costs £1834.38	Striking-off order [16 October 1996] Involved 257 prescriptions dispensed in the absence of the pharmacist
David Meddings and David Meddings Ltd Pharm J, 8 February 1997	Wolverhampton Magistrates' Court 6 June 1994 8 offences Company fined £1650; costs £1700 24 August 1992 One offence Company given absolute discharge Costs £520	Striking-off order [25/27 April 1995 and 15 October 1996] Failure to improve standards at pharmacy despite pharmacists being given one year adjournment to make improvements
Vibhuti Ralph Khan [Pharm J, 3 May 1997]	No prosecution	Reprimand [19 November 1996] Also involved failure to control medicine stocks.

1997		
David Yat Tong Lee [Pharm J, 9 August 1997]	No prosecution	Striking-off order [20 March 1997] Also involved a prosecution for the sale of Chinese medicines from endangered species

Appendix XXIV

Examples of Patient Information Leaflets

What you should know about **Erythroped® A** tablets

Please read this carefully before you start to take your tablets. If you have any questions or are not sure about anything ask your doctor or chemist.

The name of your medicine is **Erythroped® A.**
This is one of a group of antibiotics called erythromycins. Erythromycins kill bacteria which cause infections in your body.

Things to remember about Erythroped® A tablets

1 Do not take Erythroped® A if you are allergic to it or any other erythromycin.

2 Children under the age of 9 years should not take Erythroped® A tablets. Other erythromycin medicines are available for young children.

3 Look at the label on your tablets.
It will tell you when to take them.

4 Keep taking your tablets until you have finished the full course of treatment. Don't stop just because you feel better.

5 As with all medicines a few people may be upset by these tablets. See on the back of this leaflet.

6 **Keep your tablets out of reach of children.**

You will find out more about Erythroped® A tablets on the back of this leaflet.

continued

Before taking your tablets:

Has anyone ever told you that you are allergic to Erythroped® A tablets or any other erythromycin? If so, tell your doctor or chemist. You can be given another medicine instead of Erythroped® A tablets.

Taking your tablets:

You must take your tablets regularly. The label will tell you when to take your tablets. It will also tell you how many to take. Ask your doctor or chemist if you are not sure.

These tablets can be taken at mealtimes unless your doctor or chemist gives you other instructions.

Keep taking your tablets until you have finished the full course of treatment. Don't stop just because you feel better. If you stop too soon the infection may start up again because not all of the bacteria have been killed.

If you forget to take a dose take it as soon as you remember. Then go on as before. Do not take more than two tablets in any 3 hour period.

After taking your tablets:

A few people can be upset by these tablets. They may get an upset stomach, feel sick or be sick. If you suffer very badly from any of these tell your doctor.

Tell your doctor if you START suffering from rash, itching, or any other skin trouble. They may be signs of allergy.

Tell your doctor about any other unusual problems immediately.

Storing your tablets:

Keep your tablets in a safe place where children cannot reach them.
Your tablets could make them very sick.

If your doctor decides to stop treatment, return any left-over tablets to the chemist. Only keep them if your doctor tells you to.

REMEMBER: These tablets are for YOU. Only a doctor can prescribe them for you. NEVER give them to someone else. The tablets may harm them even if their symptoms are the same as yours.

Erythroped® A tablets do not contain tartrazine or other azo-dyes, lactose or gluten

The following information is required by law:

Proprietary name: Erythroped® A
Statement of Quantitative Particulars: Each tablet contains 500 mg erythromycin present as erythromycin ethylsuccinate.
Directions for use: 4 tablets a day in divided doses or as directed by the physician.
Indications: Prophylaxis/therapy of diseases caused by erythromycin-sensitive organisms.
Contraindications and Warnings Known allergy to erythromycin, caution in impaired liver function, potentiation of digoxin, warfarin, carbamazepine and theophylline.
Pharmaceutical Precautions: Store away from heat.
Product Licence Holder and Manufacturer: Abbott Laboratories Ltd., Queenborough, Kent. ME11 5EL

Provided as a public service by Abbott Laboratories 001-425-201

Eugynon® 30
Microgynon® 30

Progestogen-estrogen combinations for oral contraception

This leaflet is designed to help you use correctly Schering's 21-tablet combined oral contraceptives (combinations of two hormones) and to answer many of the questions that you may have about oral contraceptives of this type – 'the pill'. It cannot tell you everything about the pill, much of which would require explanation by your doctor to be meaningful, and much of which will not apply to you.

It is important to recognise that, however wide medical experience of a product becomes, its complete safety in all users can never be guaranteed, since every person is unique, and that with the pill, or with any other medicinal product, some risk must be accepted. The pill is available to you only on prescription because your doctor's professional knowledge and judgement are required to supervise its use. Therefore, the leaflet is not intended to take the place of his information and instructions to you, but to reinforce them. Ask him to explain anything that you do not understand, and do not hesitate to consult him if you have any doubts or anxieties about your use of the pill or the effect it may be having on you.

The benefits of combined oral contraceptives

Combined oral contraceptives reduce the risks of cancers of the ovary and the lining of the womb (endometrium) by up to a half. Benign (non-malignant) breast disease is greatly reduced. Generally, irregular periods are replaced by regular bleeding, and heavy periods by lighter bleeding. Painful periods are in most cases abolished. The symptoms that often make the last few days before a period so unpleasant a part of every month (known as the premenstrual syndrome) are commonly eliminated.

How pregnancy is prevented

From the beginning of sexual maturity until the change of life, the ovaries normally release an egg cell (ovulate) every month. If it is fertilised by a man's sperm, it becomes embedded in the womb and begins to grow. From then on, the ovaries produce increased amounts of hormone to maintain the pregnancy and to prevent further egg cells from developing. Thus, in pregnancy, development of egg cells is inhibited by the body's own hormones. Combined oral contraceptives contain similar hormones, and therefore act in a similar way, so that normally when an oral contraceptive is taken no egg cells are released for fertilisation. In addition, the fluid present in the neck of the womb remains thick, so that it is more difficult for sperms to enter the womb. Also, the lining of the womb is not prepared sufficiently for a fertilised egg to grow in it. A combined oral contraceptive thus offers protection against pregnancy in several ways.

Before starting the pill

There are certain medical conditions that rule out the use of this type of pill, which are listed later under 'Contraindications'. There are certain other conditions that, while not ruling out the pill, indicate the need for careful consideration before a decision is taken to use the pill, and which require supervision during its use. These conditions are referred to under 'Warnings' and 'Precautions'. Your doctor will have considered whether or not any of the conditions referred to under those three headings apply to you, but before you start taking the pill, if you are in any doubt, discuss the matter with him again.

How to take the pill

About the pack

This memo-pack has been specially designed to help your memory; in fact, it does the counting for you.

Each pill is placed in a section marked with the day of the week on which it should be taken.

If, at any time, you are in doubt whether you have taken your pill, a glance at the appropriate day on the memo-pack will tell you.

Taking your first course

If you are having periods as usual, take the first pill on the first day of your next period. Choose a pill marked with the correct day of the week and following the direction of the arrows, take a pill each day until the pack is empty. By starting the pill on day 1 of the menstrual cycle, additional contraceptive precautions are not required.

If you have just had a baby, it is usual to wait until your first period before starting the pill, but you should realise that it is possible to get pregnant before the first period, and use some other form of contraception in the meantime. If you are breast-feeding or want to start the pill earlier, you should get your doctor's advice.

If you are changing from another contraceptive start the pill on the first day immediately after the end of the previous oral contraceptive course, i.e. with no break between the packs.

Please note that additional precautions are needed when special circumstances reduce the reliability of the pill, as described under 'Reduced protection' (suitable methods being condoms, and cap plus spermicides). Except in those circumstances, the protection provided by the pill is continuous, and this includes the weeks between the courses of pills, when you are taking no tablets.

Subsequent courses

Leave a break of 7 days after the last tablet. Bleeding resembling a menstrual 'period' should occur when the tablets are withdrawn – that is, when the course comes to an end. It is therefore called 'withdrawal bleeding'. If a withdrawal bleed starts during the break, begin your next course after a total break of exactly 7 days.

The next paragraph tells you what to do if there is no bleeding.

Irregular bleeding

If bleeding is missed

If, as may occasionally happen, you should have no bleeding at all in the seven days after a course of pills, and you have taken the tablets correctly, it is very unlikely that you are pregnant, but the possibility should be ruled out by your doctor before you start a new course of pills. In the meantime, use condoms or a cap plus spermicide so that contraceptive protection will not be lost.

If bleeding starts while you are taking tablets

If bleeding occurs during the three weeks in which you are taking the pills, do not stop taking them. The bleeding should stop in a day or two. However, if the bleeding is troublesome, very heavy, prolonged or recurrent, you should consult your doctor. Bleeding while the pills are being taken does not mean that the pill does not suit you, nor does it necessarily mean that contraceptive protection is lost (but see 'Interaction with other medicines'). If bleeding does occur during pill-taking, it is usually only in the first two or three months, while your body is adjusting itself to the pill.

Reduced protection

If you forget to take your pill

Are you less than 12 hours late in taking one pill?

If you forget a pill take it as soon as you remember, and take the next one at your normal time. This may mean taking two pills in one day. Provided that you are no more than 12 hours late in taking the forgotten tablet contraceptive protection is not reduced.

Are you more than 12 hours late in taking one or more pills?

If you are more than 12 hours late in taking one or more pills you may not be protected. As soon as you remember take the last missed pill. This may mean taking

two pills in one day. Continue to take the pills at your normal time, and either avoid sexual intercourse or use an extra contraceptive method such as a condom for the next 7 days.

If these seven days run beyond the end of your pack, start the next pack as soon as you have finished the present one. In other words, do not leave a gap between packs.

This will mean you may not have a period until the end of two packs but this will not harm you. Nor does it matter if you have some bleeding on days when you take the pill.

If you are in any doubt about these instructions contact your Doctor or Family Planning Clinic for advice.

If you have a stomach upset

Vomiting and diarrhoea may interfere with absorption of the pill and reduce its contraceptive effect. If you do get such a stomach upset, continue to take the pills, but you should use an additional method of contraception, such as a condom or cap plus spermicide, until 7 days after you have recovered. If you come to the end of a pack in the meantime, start the next pack next day without a break.

Interaction with other medicines

Some medicines may reduce the effectiveness of oral contraceptives when taken at the same time. These include certain sedatives, antibiotics, griseofulvin, anti-epileptic and antiarthritic drugs. Suspicion that the reliability of an oral contraceptive is reduced in this way is sometimes raised by the occurrence of irregular bleeding. If you take any medicines at all while you are also taking an oral contraceptive, be sure to tell your doctor, who can advise you whether or not you should take additional contraceptive precautions.

By statute, certain information must appear in any leaflet of this kind, and must be kept seperate from the rest of the contents. That information comprises the remainder of this leaflet.

Contraindications

You should not take a combined oral contraceptive if you have any of the following: clots in the blood vessels (thrombotic disorders) or a history of these conditions or states which predispose to such diseases (e.g. disturbances of the clotting system with a tendency towards thrombosis, certain heart diseases); abnormal red blood cells (sickle-cell anaemia); high blood fats (disorders of lipid metabolism) and other conditions in which there is known or suspected to be a much increased risk of thrombosis (e.g. severe forms of the conditions referred to in paragraph 2 of 'Warnings' or the presence of a number of these conditions); a possible pregnancy; cancer of the breast or of the lining of the womb (mammary or endometrial carcinoma) or a history of these conditions; abnormal vaginal bleeding of unknown cause; a history during pregnancy of (1) itching of the whole body (pruritus of pregnancy), (2) the rash known as herpes gestationis, (3) deterioration of inherited deafness (otosclerosis), or (4) jaundice not explained by infections, poisons or obstruction of the flow of bile (idiopathic jaundice of pregnancy); certain other types of jaundice (Dubin-Johnson or Rotor syndromes); previous or existing liver tumours; short-term or severe long-term liver disease.

Warnings

There is a general opinion, based on statistical evidence, that users of combined oral contraceptives experience more often than non-users various disorders of the circulation of blood, including strokes (blood clots in and haemorrhages from the blood-vessels of the brain), heart attacks (coronary thromboses), and blood clots obstructing the arteries of the lungs (pulmonary emboli). There may not be full recovery from such disorders and it should be realised that in a few cases they are fatal. How often these disorders occur in users of modern low-dose oral contraceptives is not known, but there are reasons for suggesting that they may occur less often than with older pills.

Certain conditions carry some risk of thrombosis. They include smoking, obesity, varicose veins, some diseases of the heart and blood vessels, diabetes and migraine. In addition, if any members of your family have suffered from thromboembolic diseases (e.g. deep vein thrombosis, stroke or heart attack) at a young age, combined oral contraceptives may not be suitable for you. If any of these conditions apply to you, the advisability of your taking a combined oral contraceptive should be discussed with your doctor before you decide to take the pill. The risk of arterial thrombosis (e.g. heart attack and stroke) associated with combined oral contraceptives increases with age, and this risk is aggravated by cigarette-smoking. For this reason, the use of combined oral contraceptives by women in the older age group, especially those who are cigarette-smokers, is to be discouraged.

Many studies have looked at the risks of ovarian, endometrial, cervical and breast cancer in women using combined oral contraceptives. There is clear evidence that combined oral contraceptives offer substantial protection against both ovarian and endometrial cancer. An increased risk of cervical cancer in long-term users of combined oral contraceptives has been seen in some studies, but there is still argument about how much of this is due to the confounding effects of sexual behaviour and other factors.

The evidence linking combined oral contraceptive use and breast cancer remains unclear. The results of some studies suggest a higher risk of breast cancer presenting below the age of about 35, the risk rising with length of use. Any possible higher risk of breast cancer with combined oral contraceptives is however likely to be small and may be expected to be less with low-dose pills. The possible risk should be weighed against the many benefits of combined oral contraceptives, including their protective effects against ovarian and endometrial cancers.

The possibility cannot be ruled out that certain chronic diseases may occasionally deteriorate during the use of combined oral contraceptives. The diseases are those listed as requiring careful observation under 'Precautions'.

Benign liver tumours have been associated with the use of oral contraceptives, and malignant liver tumours have been reported on rare occasions in long-term users.

If you have pain in the upper abdomen or other symptoms that lead your doctor to examine you, and he finds signs of an enlarged liver or of bleeding inside the abdomen, he should consider the possibility of a liver tumour.

Reasons for stopping oral contraception immediately

You should take no further oral contraceptive tablets and should consult your doctor immediately if you experience any of the following: the very first attack of migraine (typically a throbbing headache and nausea, preceded by visual disturbances) that you have ever experienced; worsening of pre-existing migraine; any unusually frequent or unusually severe headaches; dizziness or fainting; sudden disturbances of vision; disturbance of speech; inflamed veins (phlebitis); pains in the chest or abdomen; swelling in the limbs; pain, tingling or numbness in any part of the body; unexplained cough; breathlessness; pain on breathing. Any of these symptoms might indicate the beginning or immediate risk of a serious thrombosis.

The risk of thrombosis is increased after many injuries, especially fractures, during and after many surgical operations, and during immobilisation, e.g. after accidents. Combined oral contraceptives should be stopped at least six weeks before planned operations, and should be stopped immediately when immobilisation (i.e. inability to move freely) is necessary.

Your doctor will probably stop the pill at once if you become jaundiced, or if he finds your blood pressure to be significantly raised, or if any of the conditions known to be capable of deteriorating during oral contraception or pregnancy (referred to under 'Precautions') should show clear signs of deteriorating.

You should stop the pill immediately if pregnancy is

diagnosed, or if there are reasonable grounds for suspecting that you may be pregnant, since it has been suggested that combined oral contraceptives, in common with many other substances, might be capable of affecting the normal development of the child in the early stages of pregnancy. It can be definitely concluded, however, that, if a risk of abnormality exists at all, it must be very small.

Precautions
Examination of the pelvic organs, breasts and blood pressure should precede the prescribing of any oral contraceptive, and should be repeated regularly.

The following conditions require careful observation while you are taking the pill: a history of severe depressive states, varicose veins, diabetes, high blood-pressure (hypertension), fits (epilepsy), the inherited form of deafness known as otosclerosis, the disease of the nervous system called multiple sclerosis, the inherited metabolic disease called porphyria, calcium deficiency with cramps (tetany), disturbed liver function, gall-stones, diseases of the heart and blood vessels (cardio-vascular diseases), kidney diseases, brown patches on the face and body such as occur during pregnancy (chloasma), fibroids of the womb, asthma, the wearing of contact lenses, or any disease that is prone to worsen during pregnancy (your doctor can explain any of these terms that you do not understand). The worsening or first appearance of any of these conditions may indicate that the oral contraceptive should be stopped.

The risk of the deterioration of chloasma, which is often not fully reversible, is reduced by the avoidance of excessive exposure to sunlight.

Side-effects
Occasional side-effects may include nausea, vomiting, headaches, breast tension, changes in body weight or interest in sex (libido) and depressive moods: possible deterioration or recurrence of the conditions mentioned in paragraph 2 of 'Precautions'.

It is not easy to decide whether or not something that you notice is the result of your taking the pill, since among millions of women during long periods of treatment many symptoms are bound to occur that are quite unconnected with the use of the pill. Studies comparing oral contraceptives with dummy tablets have suggested that true side-effects felt by the users are few, and are mainly short-lasting.

However, such studies may not detect rare or long-term side-effects. Most known or suspected side-effects are of a minor nature and are reversible, but not all. Ask your doctor about any change in your health or general sense of well-being that you notice while taking an oral contraceptive.

Presentation
Each tablet of Eugynon 30 contains 0.25 mg levonorgestrel and 0.03 mg ethinyloestradiol (INN ethinylestradiol).

Eugynon 30 also contains the following inactive ingredients: Lactose, maize starch, povidone 25 000, povidone 700 000, magnesium stearate, sucrose, polyethylene glycol 6 000, calcium carbonate, talc, wax E.

Each tablet of Microgynon 30 contains 0.15 mg levonorgestrel and 0.03 mg ethinyloestradiol (INN ethinylestradiol).

Microgynon 30 also contains the following inactive ingredients: Lactose, maize starch, povidone 25 000, povidone 700 000, magnesium stearate, sucrose, polyethylene glycol 6 000, calcium carbonate, talc, glycerin, wax E, colours E171, E172.

Store all drugs properly and keep them out of reach of children.

The product licences are held by
Schering Health Care Ltd, Burgess Hill, West Sussex.

Product licence numbers
Eugynon 30: 0053/0049
Microgynon 30: 0053/0064

Eugynon 30 and Microgynon 30 are manufactured by SCHERING AG Germany

Your Prescription for Retrovir* Capsules

0/5828

Wellcome

Please read this carefully before starting treatment.
If you have any doubts or worries, or you are simply not sure about something, consult your doctor.

Questions you should ask yourself before taking Retrovir:

- Have you previously experienced an allergic reaction to zidovudine?
- Do you suffer from any blood disorder, eg anaemia?
- Are you currently taking, or likely to be taking, any other medicines, including remedies you can buy yourself such as paracetamol, aspirin or codeine?
- Are you pregnant, trying to become pregnant or breast-feeding?
- Do you suffer from liver or kidney disease?

If the answer is YES to any of these questions, and if you have not already discussed them with your doctor, go back to him BEFORE starting treatment.

What is Retrovir treatment and how does it work?

Retrovir is the brand name for the drug zidovudine, sometimes known as AZT. It belongs to a group of medicines called antivirals. It is used to delay the progression of HIV infection. In order to understand how Retrovir works, it will help you to know how HIV multiplies within the body.

HIV reproduces itself by entering CD4 cells and turning them into 'mini factories' producing more viruses which, in turn, infect more cells. If this process goes untreated, eventually there are too few CD4 cells left to fight off diseases and infections - a condition which usually leads to AIDS.

Retrovir does not kill HIV, but works by entering the CD4 cells infected with it, helping to stop the production of new viruses and their despatch to other cells. Retrovir therefore helps to preserve your ability to resist disease by helping to prevent further deterioration of the immune system.

Taking your medicine

- It is important to take your medicine as directed by your doctor. The label should tell you how much to take and how often. If you're not absolutely sure, consult your doctor.
- The dose prescribed will vary from patient to patient and will depend on a number of factors, including the stage of infection. In practice a total daily quantity of between 500mg and 1000mg is usually prescribed divided into appropriate doses.
- The capsules should be swallowed whole with some water.
- If you forget to take a dose, don't worry. Simply take it as soon as you remember and then continue as before.
- If you think you may have difficulty in remembering to take your capsules at the times specified, it's a good idea to use a pocket timer or wrist-watch alarm to remind you.
- Whilst accidentally taking a larger dose than prescribed is not likely to cause any untoward effect, you should let your doctor know as soon as possible in such a situation.
- Because your medicine controls and does not cure your condition, you will normally need to take it continually. You should not stop treatment unless your doctor tells you to.
- Remember that treatment with Retrovir does not reduce the risk of passing HIV on to others by sexual contact or blood transfer, so you will remain infectious whilst taking the capsules.

After taking your medicine

- Retrovir is normally well tolerated, particularly by patients with early HIV infection. However, because of the way it works, it may sometimes cause side effects of which there are two main types, as follows;

1) The first can occur during the first 4 to 5 weeks of treatment and consists of nausea, vomiting and headache. Very rarely, muscular aches and a rash may also develop. In the vast majority of cases, all these effects disappear on their own after a few weeks, a fact worth bearing in mind if you experience them. Check with your doctor if they do not go away or become distressing.
2) The second can develop after four to six weeks of treatment and affects your bone marrow's production of blood cells. Most commonly, production of red blood cells is reduced, resulting in anaemia. If this happens, the symptoms are tiredness and shortness of breath. Also, less commonly, the production of a

continued

type of white blood cell may be reduced which can make you more prone to infections. Studies have shown that these side effects occur in 5% or less of patients being treated for early HIV infection.

- These effects are generally reversible and it is important to note that, with the lower treatment doses currently being prescribed, anaemia is now less common than when Retrovir was first introduced.
- If you experience either type of the side effects associated with Retrovir, consult your doctor. He is likely to either reduce your dose or temporarily interrupt your treatment, usually for between two and four weeks, in order to allow your blood time to recover.

Can I take other medication whilst on treatment?

- You can assume that any medication prescribed by a doctor who has full knowledge of your condition and treatment will be safe to take along with Retrovir.
- In fact, as part of your treatment, your doctor may offer you other medication to treat or prevent the opportunistic infections that may occur.
- Problems can arise with medication that has not been prescribed by your doctor but which you may be in the habit of using or consider taking.
- Taking any of these medications, eg paracetamol, along with Retrovir, without your doctor's knowledge may be harmful. This is because some preparations can interact adversely with Retrovir and make side effects worse if taken at the same time.
- However, few adverse reactions have been noted by patients who take vitamin supplements, herbal remedies or homeopathic medicines, so if you feel benefit from these, continue taking them but keep your doctor informed.

Is it safe to drink alcohol whilst on treatment?

- Alcohol can affect your response to many medications and you should discuss this matter in more detail with your doctor who will be familiar with your own particular case. Remember that excess alcohol in general can affect your overall health.

What about Retrovir in pregnancy?

- The effects of Retrovir in pregnancy are not yet known. It is also not known if it is present in breast milk. HIV positive women who become pregnant, who are thinking of having a child or who are breast feeding should always consult their doctor.

Is there anything else I should know?

- It is important to understand that Retrovir can delay and slow down the progression of HIV infection, but you must be aware of the possibility of eventually developing symptomatic infection.
- Resistance of the virus to Retrovir has been shown in a number of people and is more frequent in those with symptomatic infection. The importance of this in the overall future progression of the virus is not at present known.

Storing your medicine

- Keep your capsules in a cool, dry, dark place and out of the reach of children.
- If your doctor decides to stop and not restart your treatment, return any left over capsules to your pharmacist for disposal. Only keep them if your doctor tells you to.

What's in your medicine

- Retrovir Capsules contain zidovudine. The all-white capsules contain 100 mg and the blue and white capsules 250 mg.

REMEMBER: THIS MEDICINE IS FOR YOUR USE ONLY.
Never give it to others as it may harm them even if their symptoms are the same as yours.

Product Licence for Retrovir Capsules is held by the Wellcome Foundation Limited, London, NW1 2BP.
The Product Authorisation for Retrovir Capsules in Ireland is held by Wellcome Ireland Limited, Dublin.
This information has been prepared in accordance with guidance issued by the Association of the British Pharmaceutical Industry. It applies only to Retrovir Capsules.

*Trade mark

0/5628 83.11

Zantac Tablets 300mg

Trade mark

Please read this information carefully before starting to take these tablets.

● WHAT YOUR TABLETS DO

Zantac Tablets contain ranitidine, one of a group of medicines called H_2 antagonists. They cut down the amount of acid in your stomach, which can make the following medical conditions better:

- Ulcer disease of the stomach, or the part it empties into, the duodenum.
- Problems caused by acid in the gullet (oesophagitis).
- Other problems like these which can cause pain or discomfort sometimes known as "indigestion", "dyspepsia" or "heartburn".
- Some medicines for arthritis can cause ulcers as a side effect - if you are on this sort of treatment your doctor may have prescribed Zantac Tablets to try to keep you free of ulcers.

If you are not sure why you are taking these tablets ask your doctor.

● BEFORE YOU TAKE YOUR TABLETS

If you have been told you are allergic to Zantac or ranitidine, or
If you think you may be pregnant,
or
If you are breast-feeding,
or
If you have been told you have a rare condition called porphyria.
Does the doctor who prescribed them know this?
If not, tell your doctor before taking any tablets.
Even so your doctor may still want you to take them.

● TAKING THE TABLETS

Look at the label - it should say who should take them, how many and when. If it does not, or you are not sure, ask your doctor or pharmacist.

The usual dose is one at night or up to one twice a day.

To help you remember to take the tablets they are sealed in a special kind of pack. Read the instructions on this pack before starting your tablets.

Swallow each tablet whole with a drink of water.

● AFTER STARTING YOUR TABLETS

After a few days you should feel much better but do not stop taking the tablets or the pain and discomfort may return. Most people taking this medicine find it causes no problems. As with most medicines, a few people may find they have side effects from it.

See across for more information.

● WHERE TO KEEP YOUR TABLETS

Keep Zantac Tablets away from heat which could spoil them. As with all medicines, keep these tablets safely away from children. A child may be harmed by medicine prescribed for someone else.

● WHAT TO DO IF YOU MISS A DOSE

If you forget to take a dose, take another as soon as you remember. Then go on as before.

● WHAT TO DO IF YOU TAKE TOO MANY TABLETS

It is important to stick to the dose on the label of your medicine. Taking more than this is unlikely to be dangerous unless many tablets are taken at once.

In that case, do not delay; ask your doctor what to do or contact your nearest hospital emergency department.

● BREAST FEEDING

Although ranitidine from Zantac Tablets gets into mother's milk, it is unlikely to cause problems, but remember to tell your doctor if you are breast feeding.

● IF YOU DON'T GET BETTER

If you have taken all the tablets and you still feel unwell, or if you have not taken all the tablets but feel worse, tell your doctor.

● WHAT TO DO WITH UNUSED TABLETS

If your doctor stops your treatment, return any unused tablets to a pharmacist for safe disposal.

Do not take the tablets after the date on the carton or wallet. Only keep your tablets if your doctor tells you to.

● REMEMBER

This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. There may be reasons why it could harm that person.

● SIDE EFFECTS

Along with its needed effects, a medicine may cause unwanted effects. Most people taking this medicine find it causes them no problems.

A few people can be allergic to some medicines; if any of the following side effects come on soon after taking these tablets, stop the tablets and tell your doctor immediately:

- Sudden wheeziness or tightness in the chest.
- Swelling of eyelids, face or lip; with or without a lumpy skin rash ("hives") anywhere on the body.

Also check with your doctor as soon as possible if any of these uncommon side effects are noticed:

Rare
- Skin rash (red spots)
- Jaundice (yellow colour of skin)
- Confusion.

Also check with your doctor at your next visit if any of these side effects are noticed:

Uncommon	Rare
● Headache	● Pains in muscles or joints
● Dizziness	● Feeling of depression

If you are unwell or have any unusual discomfort you do not understand tell your doctor.

H0239 0493

continued

Zantac Tablets 300mg

Trade mark

Use only as directed by the physician
Store below 30°C
Keep all medicines out of the reach of children

● WHAT YOUR TABLETS CONTAIN

Ingredients of each white, capsule-shaped tablet include:
The active ingredient - ranitidine (as hydrochloride) 300mg.
Other ingredients include microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hydroxypropylmethylcellulose (E464), triacetin and titanium dioxide (E171).

● FURTHER INFORMATION

Not all the information about your medicine is printed here or inside. If, after reading this information, you have any questions or are not sure about anything, ask your doctor or pharmacist who has the information you need and will advise you.

Pharmaceutical Companies are not allowed to answer questions from patients about their diseases. You may well be able to find out more about prescribed medicines from books in public libraries. This information has been provided in accordance with guidance issued by the Association of the British Pharmaceutical Industry.

The information provided applies only to Zantac Tablets 300mg.
Information written March 1993

PL10949/0043 POM

ZANTAC is a trade mark.

Product licence held by Glaxo Pharmaceuticals UK Limited, Stockley Park, England
Manufactured by Glaxo Pharmaceuticals UK Limited, Speke, Liverpool, England

On behalf of Glaxo Laboratories Limited, Stockley Park, England UB11 1BT

Appendix XXV

European Public Assessment Report for Rilutek

The European Agency for the Evaluation of Medicinal Products

10 June 1996
Rev. 2, 17 October 1997
CPMP/290/96

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR) *

RILUTEK

International Non-proprietary Name (INN): **Riluzole**

Abstract

On 10 June 1996, the European Commission issued a marketing authorisation valid for the European Union for the medicinal product Rilutek, which contains Riluzole. This decision was based on the favourable opinion and on the assessment report adopted by the Committee for Proprietary Medicinal Products (CPMP) on 14 February 1996. The pharmaceutical company responsible for this medicinal product is Rhône-Poulenc Rorer, France.

Riluzole is authorised for the treatment of patients with amyotrophic lateral sclerosis (ALS), a neurological disease, leading to progressive muscle weakness. Detailed conditions for the use of this product are given in Annex I of the CPMP Opinion, the Summary of Product Characteristics (SPC), which can be found in this EPAR and is available in all European Union official languages.

The active substance of Rilutek, Riluzole, is thought to demonstrate its effect via a neuroprotective action exerted at the cellular (neuronal) level.

Clinical trials designed to investigate Rilutek have demonstrated that it induces a modest extension of life or the time taken for the progression of the disease to require mechanical ventilation, in ALS patients other than those who are in the late stages of the disease. These studies showed that Rilutek was effective only in patients having ALS, but not other forms of motor neuron disease. There is no evidence that Riluzole exerts a therapeutic effect on motor function, lung function, fasciculations, muscle strength and motor symptoms.

The most frequent adverse reactions observed during treatment were asthenia, nausea and elevations in parameter values measured by liver function tests. Riluzole appears in some cases to damage liver cells and structure and may cause liver dysfunction. Other commonly reported side effects include abdominal pain, headache, vomiting, increase of heart rate, vertigo, alteration of the sensibility in the skin area surrounding the mouth.

The CPMP, on the basis of the efficacy and safety data submitted, considered that Rilutek showed adequate evidence of efficacy and a satisfactory safety profile and therefore recommended that the Marketing Authorisation should be granted.

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* The European Public Assessment Report (EPAR) reflects the scientific conclusion reached by the Committee for Proprietary Medicinal Products (CPMP) at the end of the centralised evaluation process and provides a summary of the grounds for the CPMP Opinion in favour of granting a marketing authorisation for a specific medicinal product. It is made available by the EMEA for information to the public, after deletion of commer-cially confidential information. The legal basis for its creation and availability is contained in Article 12 (4) of Council Regulation (EEC) No. 2309/3.
The content of the EPAR is derived from the various reports produced during the centralised evaluation procedure, resulting from the review of the application submitted by the applicant, together with the scientific discussion at CPMP meetings. The EPAR will be updated as appropriate throughout the authorisation period as changes to the original terms and conditions of the authorisation (i.e. variations, pharmacovigilance issues, specific obligations) are made.

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MARKETING AUTHORISATION NUMBERING SYSTEM
ADOPTED BY THE EUROPEAN COMMISSION

RILUTEK

EMEA APPLICATION No.	CPMP OPINION No.	COMMUNITY REGISTER OF MEDICINAL PRODUCTS No	MEDICINAL PRODUCT STRENGTH AND PHARMACEUTICAL FORM
EMEA/H/C/109/00/00	CPMP/132/96	EU/1/96/010/001	50 mg coated tablet

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N.B. The abstract and the full text of the CPMP opinion are available in all eleven official languages of the European Union

I BACKGROUND INFORMATION ON THE PROCEDURE

1. Submission of the dossier

The company Rhône-Poulenc Rorer, France, submitted on 3 July 1995, to the European Agency for the Evaluation of Medicinal Products (EMEA), an application to obtain marketing authorisation for the medicinal product Rilutek in accordance with the Centralised Procedure falling within the scope of Part B of the Annex to Council Regulation No (EC) 2309/93 of 22 July 1993.

The Rapporteur and Co-R apporteur appointed by the CPMP and their evaluation teams were as follows:

Rapporteur:	Dr. D. Jefferys	Co-Rapporteur:	Dr. P. Le Courtois
Evaluators:	Dr. A. M. French Dr. R. Lee Prof. J. A Lewis Dr. J. B. Warren	Evaluators:	Dr. E. Abadie Dr. P. Lefevre Dr. M. H. Tissier

2. Steps taken for the assessment of the product

- The Co-Rapporteur's initial assessment report was circulated to all members of the CPMP on 25 September 1995.
- The Rapporteur's initial assessment report was circulated to all members of the CPMP on 27 September 1995.
- The CPMP during their meeting on 17-19 October 1995, considered the methodological problems concerning design, execution and statistical analysis of the clinical part and proposed an expert meeting on the 15 November 1995, with experts on neurology and statistics. A list of points to be answered by the company in advance of that meeting was also agreed and sent to the company on 20 October 1995.
- A summary of the current status of methodological issues relating to efficacy was issued on 27 November 1995.
- The CPMP final consolidated list of comments was sent to the company on 30 November 1995.
- The company submitted the responses to the consolidated CPMP list of comments on 22 December 1995.
- A Rapporteur/Co Rapporteur expert meeting was held on the 15 January 1996, to finalise the assessment report on the company's responses.
- The Rapporteur's "Responses' assessment report" was circulated to all CPMP Members on 16 January 1996.
- The Co-Rapporteur's "Responses' assessment report" was circulated to all CPMP Members on 19 January 1996.
- The CPMP in their meeting on 13-15 February 1996 discussed the recommendations presented by the Rapporteur and Co-Rapporteur. A hearing with the company took place on 13 February 1996 to address the final outstanding issues.
  Amendments were made accordingly on the Summary of Product Characteristics and User Package Leaflet texts.
- The CPMP on 14 February 1996 adopted a favorable opinion by scientific consensus.

3. Steps taken after granting the initial Marketing Authorisation

On 13 September 1996, the Marketing Authorisation Holder submitted two Type I Variations in accordance with Commission Regulation (EC) No. 542/95. These variations related to a new analytical method for assay and determination of related substances in the active substance and the medicinal product. On 23 October 1996, the EMEA approved these variations, which do not require an amendment to the Commission Decision. The relevant changes, following these variations, have been made in section III.2 of the EPAR.

On 25 April 1997, the Marketing Authorisation Holder submitted a Type II Variation in accordance with Commission Regulation (EC) No. 542/95. This variation concerned amendments of sections 4.2, 4.4 and 5.2 of the SPC in accordance with the recommendation of the CPMP following evaluation of follow-up measures submitted by the Marketing Authorisation Holder in December 1996. On 18 June 1997, the CPMP adopted a positive opinion on this Type II variation, and the respective Commission Decision was issued on 8 October 1997. This variation required amendments of section III. 4 'Pharmacokinetic studies' of the EPAR.

II GENERAL CONDITIONS FOR THE MARKETING AUTHORISATION

1. Manufacturing Authorisation Holders

Manufacturer of the active substance:

RHÔNE-POULENC RORER - Centre de production de Vitry, Villeneuve, 9 quai Jules-Guesde - 94403 VITRY-SUR-SEINE, FRANCE.

Manufacturer of the finished medicinal product and responsible for batch release:

RHÔNE-POULENC RORER Pharmaceuticals Limited, Linsbunny Industrial Estate, Nenagh, Co. Tipperary, Ireland.

Manufacturing licence issued on 4 June 1993, by the Department of Health (Public Health Division) Hawkins House, Dublin 2, Ireland.

2. Conditions or restrictions regarding supply and use

Medicinal product subject to non-renewable restricted medical prescription.

III SCIENTIFIC DISCUSSION

1. Introduction

Rilutek tablets contain riluzole, a new chemical entity of the benzothiazole class. Riluzole is indicated for the treatment of patients with amyotrophic lateral sclerosis (ALS) . The indication is based on data derived from two pivotal clinical trials in which it has been demonstrated that riluzole induces a modest extension of the life of patients with ALS regardless of the onset type. The claimed indication for this medicinal product is :"To extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS)".

ALS is a progressive degenerative disorder of motor neurons and motor cortex. The symptoms of ALS are characterised by a progressive and irreversible decrease of muscle strength. The following definition of the pathology of ALS is found in the Oxford Textbook of Medicine: "a disease in which degeneration affects motor neurons in the anterior horns of the gray matter of the spinal cord, in certain somatic motor nuclei of the cranial nerves and in the cerebral cortex. There is no inflammatory reaction and microscopy provides no clue to the cause of the initially asymmetrical but progressive neuronal loss. As both upper and lower neurons are affected to varying degrees in different patients, the symptomatology is diverse." The disease has a unremitting course of wasting and weakness and is usually fatal within three years.

Although the pathogenesis of ALS is not completely elucidated and no validated models exist in which riluzole may be tested, it is suggested that glutamate (the primary excitatory neurotransmitter in the central nervous system) plays a role for cell death in the disease. Riluzole is proposed to act by inhibiting gluatmate processes. The mode of action is unclear.

2. Overview of part II of the dossier: chemical, pharmaceutical and biological aspects

The pharmaceutical data described in Part II of the dossier are summarised below.

Synthesis:

The synthesis route comprises 5 steps beginning with the nitration of the starting material trifluoromethoxybenzene. Control during the first three steps was by a GC method and the fourth and fifth steps by an HPLC (CN reverse phase) method. Satisfactory information has been provided on the in-process control methods and satisfactory specifications are shown to be applied for control of the intermediate products. Satisfactory specifications and details on the control tests implemented were provided for the materials contributing to the structure of the final molecule and for the other reactants, reagents and solvents.

The analytical methods employed (GC, TLC, HPLC) were found to be capable of controlling the drug substance within its design specification. Drug substance specification was controlled by testing appearance, identity, color, melting point, particle size distribution, water content, appearance and color of methanolic solution, sulphated ash, heavy metals and related substances assays.

Proof of structure was provide by elemental analysis, UV and IR spectroscopy, EI and CI mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy. Satisfactory spectral interpretations have been provided and appear to be consistent with the proposed molecular structure.

The physicochemical attributes of the molecule are adequately presented. The parameters studied included solubility (in methanol, HCl and water), melting point, pK, partition coefficient and polymorphism. X-ray diffraction examination of 5 industrial batches showed no evidence of polymorphism.

A comprehensive study on potential impurities is presented. Impurities related to residual solvents, related substances arising from the synthesis (including intermediates and secondary reaction products), degradation products (monitored by stress testing; heat, light, acid, alkali and peroxide stress in organic and aqueous solutions) were addressed adequately. The drug substance was found to be extremely stable, with only two significant degradation products being observed when riluzole was in solution in acetone and exposed to light. Degradation impurities were not

found in normal conditions. Batch analyses were performed on 24 batches of material, ranging in size from 300g to 55.6kg (production scale), used in preclinical and clinical studies. Stability data were generated on 6 batches of drug substance, 3 pilot and 3 production. No deviations from initial values for assay or related substances were observed. The data support the proposed storage period of 24 months before re-test. Real-time studies are on-going to confirm the stability of the active drug substance over 24 months.

Dosage form:

The core of each tablet contains 50 mg of active drug substance and the excipients, anhydrous dibasic calcium phosphate, microcrystalline cellulose, anhydrous colloidal silica, magnesium stearate and croscarmellose sodium. All the excipients used have been shown to comply with the most stringent pharmacopoeial requirements available, primarily with the European Pharmacopoeia.

The active drug substance was found to have local anesthetic actions and this necessitated film coating the product. The core is film coated, comprising hydroxypropylmethylcellulose, polyethylene glycol 6000, titanium dioxide and purified water.

Three formulations are described. Initial manufacturing development centered around a water/alcohol/povidone wet granulation process (A) which produced a product for use in early clinical studies. Subsequently a move to direct compression formulations (B) based on dibasic calcium phosphate and microcrystalline cellulose was made and the third formulation is the marketing formulation (C) which is also produced by direct compression. The account of the qualitative and quantitative optimisation of the formulation selected for development appears convincing and the arguments put forward are sound. There was concern over the possible lack of clinical efficacy due to the differences in C_{max} of the formulations B and C in the dose ranging study 301; justification was based on the safety data collected with the 200mg dose in study 301.

Pilot scale batches were manufactured using different input batches of active drug substance and excipients to validate the robustness of the formulation process, to identify the critical process parameters and to determine appropriate in-process controls. Suitable controls were applied to the powder blend, the tablet cores and the coated tablets.

In vitro dissolution was not influenced by the particle size. Comparative *in vitro* dissolution profiles of 3 industrial scale batches (produced at the intended manufacturing site) and two development batches, demonstrated no significant differences in release characteristics.

Validation data were provided on 3 full-scale production batches. Full details are provided on blending conditions, batch identification of input material, compression and coating. Overall it is concluded that the manufacture is sufficiently robust to provide assurance that the process produces tablets of consistent quality complying with the design specification.

Finished product specification was controlled by testing appearance, color, identification (HPLC, IR) and assay and related substances (HPLC) of riluzole, identification of titanium dioxide, uniformity of content, dissolution and microbiological quality. The total related substances limit is proposed nmt 0.8% which is made up of synthetic impurities and potential degradation products.

Satisfactory batch analyses data were provided on 4 full-scale production batches manufactured at the intended production site.

Stability data were generated on 4 pilot batches and 3 production batches of tablets stored in the PVC/aluminium blisters intended for the marketed product. No significant changes from initial values were noted for production scale product stored under all storage conditions. Overall, the product exhibits a good stability profile and the data, as presented supports the proposed shelf life of 24 months. It was agreed that no special storage instructions should apply to Rilutek.

3. Overview of part III of the dossier: toxico-pharmacological aspects

The preclinical dossier is extensive and complies with GLP standards except for some early studies which have no major significance for the assessment.

Pharmacodynamics

Riluzole has been shown to cross the blood brain barrier and to be active in various in vivo experimental models of neuronal injury involving excitotoxic mechanisms such as cerebral ischemia. Riluzole in vitro, protects cultured rat motorneurones from the excitotoxic effects of glutamic acid and prevents the death of cortical neurons induced by anoxia. In vitro and animal model studies have shown that riluzole is able to modify neurotransmission mediated by glutamate, particularly in circumstances where overstimulation of the post-synaptic nerve occurs.

Summarised below is a list of its activities (derived from the primary pharmacological studies) which led to the rationale for progressing this compound to clinical trials:

- Protection against neurotoxicity in rat brain slices exposed to depolarising agents acting at excitatory amino acid receptors.
- Protection against anoxia or glutamate toxicity in cultured motor neurones.
- Protection of rat cortical neurones against toxic factors in CSF from patients with ALS

It should be noted however that there were no validated animal models of ALS in which to test Riluzole.

Effects of riluzole unrelated to the desired use include muscle relaxation and sedation (through depression of CNS activity) in rodents, but not neuroleptic, anxiolytic or psychostimulating activity in usually sensitive models. At 2 mg/kg i.v and above, EEC and sleep patterns were found to be changed. Although the action of riluzole on voltage-dependent sodium channels may have consequences on cardiac function, no cardiovascular effects of significance were seen at 3 mg/kg in rats. The local anaesthetic action observed at > 1mM concentrations could be the result of riluzole's action at these ion channels. Riluzole showed no anticholinergic action and only transient effects on dog respiratory function at doses of 2 mg/kg and above.

Of the 7 metabolites examined, only 2 (the 5-hydroxy- and hydroxylamine compounds) retained some of the qualitative pharmacological properties of riluzole. No new interactions with receptor binding sites were found. The maximum concentrations of the metabolites were considered to be too low to be of importance.

Pharmacokinetics

Pharmacokinetics were studied in the mouse, rat, rabbit, monkey and dog.

The use of radiolabelled riluzole showed that absorption from the GI tract was efficient but variable in all species. A high oxidative hepatic metabolism was evidenced in all species, the elimination of metabolites occurring mainly through urinary tract. Distribution to body tissues was extensive, with CNS concentrating radioactivity some threefold over plasma level within 1 hour of a single dose. However, tissue retention was low and by 72 hours after dosing radioactivity was only significant in the organs associated with excretion, plus a small residuum bound to melanin. Repeated administration of radiolabelled riluzole identified thyroid, adrenals, and skin as retainers of concentrations higher than those of plasma for at least 7 days.

Radioactivity in rat fetuses and milk confirmed the wide distribution property of riluzole. However, kinetics in pregnant animals was not significantly different.

The formation of a ureido metabolite (RP 69597) in monkey (3%) and man (10%) is also mentioned in this dossier although no mention is made whether this metabolite might be a possible cause of adverse effects at levels of riluzole beyond that for the desired activity.

Possible interaction kinetics have been suggested for compounds such as amitryptiline, clomipramine, diazepam and diclofenac, but the in vitro inhibition constants for these substances indicate that in vivo interactions are unlikely to be of clinical importance.

Toxicology

Single dose studies:

Acute toxicity was related to the CNS impact of riluzole. The dose-response relationship indicated a steep slope from mild lethargy, plus effects on respiration and CV function, to lethality.

Repeated administration studies:

In i.v or oral studies lasting from 14 days to 6 months, the clinical signs of toxicity were attributed to CNS reactions resulting from the excessive inhibition of the transmission processes, which were manifest as salivation and lack of co-ordination followed by sedation, lethargy, reduced activity, prostration and eventual mortality.

Reductions in red blood cell parameters and/or alterations in liver parameters without histology impairment were noted in subacute and chronic toxicity studies in rats and monkeys. In dogs haemolytic anaemia was observed.

In a single toxicity study, the absence of corpora lutea was noted at a higher incidence in the ovary of treated compared to control female rats. This isolated finding was not noted in any other study or species.

On the basis of toxicology studies, liver, blood and ovarian cells can be regarded as three potential target organs.

Reproductive toxicology:

Doses of 8 mg/kg/day had no adverse effects on reproduction and development in rats although at 15 mg/kg/day (which is higher than the recommended human dose), adverse effects including mortality, loss of implantation in survivors, reduced reproductive performance and fertility and toxicity in offspring during lactation were observed.

Teratogenicity tests:

Standard design teratogenicity tests showed no evidence that riluzole could cause malformation or malfunction in fetuses of rats or rabbits.

Conventional genotoxicity: *in vitro* assays; utilising rat liver S9 fraction to model metabolism, gave no evidence of genotoxic potential for riluzole. In vivo assays in rat and mouse also gave no indication of chromosomal damage. There remains the possibility that these models did not generate all metabolites relevant to humans, particularly since no metabolic characterisation of the S9 fraction was conducted.

Carcinogenic potential: Two rodent carcinogenicity assays are ongoing.

Special toxicity studies: Riluzole has been shown to induce haemolytic anaemia in dog. Various possible mechanisms of action have been investigated, but no alterations were found in different red blood cell parameters (electrolyte content, osmotic fragility etc.).

No haemolytic potential has been shown in vitro on human, monkey, rat and dog erythrocytes.

A bromo derivative, seen as a significant impurity, was not mutagenic in a standard Ames test and not more acutely toxic than riluzole in mice.

Exposure of the environment to Rilutek is not considered to be a concern as judged from the risk assessment supplied.

4. Overview of part IV of the dossier: clinical aspects

Tolerance and pharmacodynamics studies

Changes were recorded in the EEG spectrum, proving that Riluzole crosses the brain barrier. Although somnolence was the most common dose-dependent CNS side effect observed, Riluzole did not affect the sleep profile. No significant changes in the psychomotor performances were observed in studies carried out on 129 healthy volunteers involved in 7 studies except the vigilance which was sometimes decreased at high doses.

In one study in healthy volunteers, therapeutic doses of riluzole reduced significantly the EEG alterations caused by hypobaric hypoxia simulating an altitude of 5000 m. In another study, riluzole had no effect on similar parameters measured in healthy volunteers in a model of hypoxia corresponding to an altitude of 6000 m. Riluzole has also been shown to moderately reduce the cerebral metabolism of glucose in some regions of the brain as shown by Pet-scan.

Pharmacokinetics studies

About 350 subjects were enrolled in 16 studies. In most of the studies Riluzole was given via the oral route of administration.

The pharmacokinetics of riluzole have been evaluated in healthy male volunteers after single oral administration of 25 to 300 mg and after multiple-dose oral administration of 25 to 100 mg bid. The pharmacokinetics of riluzole were also studied in healthy elderly, as well as in subjects with impaired renal or hepatic function. In healthy volunteers, plasma levels increase with the dose and the pharmacokinetic profile is dose-independent and shows a linear PK behavior.

With multiple dose administration (10 day-treatment at 50 mg riluzole bid), unchanged riluzole accumulates in plasma by about 2 fold and steady-state is reached in about 5 days.

Administering oral dosing of 25, 50 or 100 mg twice daily, the elimination half-life of riluzole ranges from 9-15 hours with a steady state plasma concentration being reached at 3-8 days. In clinical study 301 the clearance of riluzole remains stable over time up to month 10. No accumulation of the drug with time was observed.

Absorption

Riluzole is rapidly absorbed after oral administration with maximal plasma concentrations occurring within 60 to 90 minutes (Cmax = 173 ng/ml). About 90% of the dose is absorbed and the absolute bioavailability is 60%. The rate and extent of absorption is reduced when riluzole is administered with high-fat meals (decrease in Cmax of 44%, decrease in AUC of 17%).

Distribution

Riluzole is extensively distributed throughout the body and has been shown to cross the blood brain barrier. The volume of distribution of riluzole is about 245 l (3.4 l/kg). Riluzole is about 97% protein bound and it binds mainly to serum albumin and to lipoproteins.

Metabolism

Unchanged riluzole is the main component in plasma and is extensively metabolised by cytochrome P450, with subsequent glucuronidation. In vitro studies using human liver preparations demonstrated that cytochrome P450 1A2 is the principal isoenzyme involved in the metabolism of riluzole. The metabolites identified in urine are 3 phenolic derivatives, one ureido-derivative and unchanged riluzole. The pharmacokinetics and biological activity of the metabolites have not been investigated. About 20 metabolites of riluzole are found in urine.

Excretion

Less than 1% of riluzole is excreted unchanged. Most of the substance is converted to glucurono-conjugated derivatives (pathway through cytochrome P450 1A2 and UDPG-T)). The overall urinary excretion accounts for about 90% of the dose. Glucuronides accounted for more than 85% of the metabolites in the urine.

Special populations

The pharmacokinetic parameters of riluzole after multiple dose administration (4.5 days of treatment at 50 mg riluzole bid) were not affected in elderly healthy volunteers (> 70 years). Thus, there are no special instructions for the use of riluzole in this population.

There was no significant difference in pharmacokinetic parameters between patients with moderate or severe chronic renal insufficiency (creatinine clearance between 10 and 50 ml.min^{-1}) and healthy volunteers after a single oral dose of 50 mg riluzole. However, since repeated dose administration has not been studied in subjects with renal impairment, treatment of this population is not recommended.

The AUC of riluzole after a single oral dose of 50 mg, increased by about 1.7 fold or 3 fold in patients with mild chronic liver or moderate chronic liver insufficiency, respectively. Riluzole is contraindicated in patients who have hepatic disease or have baseline transaminases greater than 3 times the upper normal limit.

Efficacy studies.

Three randomised controlled trials have been reported, referred to as trials 216, 301 and 302.

Two strata were defined a priori in the study designs: Amyotrophic Lateral Sclerosis (ALS) of limb or bulbar onset.

Trial 216 was the first trial and compared 100 mg of Rilutek with placebo; trial 301 was a dose-response trial comparing 3 doses with placebo and was considerably larger; trial 302 was a comparison of 100 mg with placebo in patients ineligible for trial 301. In the three studies, survival, defined by patients who were alive, or not intubated or not tracheotomised was the primary efficacy endpoint. Secondary end-points were functional scores (MRC, NORRIS).

In study 216, patients with Amyotrophic Lateral Sclerosis of bulbar onset survived longer on Rilutek whereas in study 301, the two Rilutek treated groups showed a marginally longer survival than placebo treated patients, and no effect on survival was shown in study 302. On this basis, taking also into consideration the absence of any evidence of efficacy on symptoms of the disease, concerns were expressed on the robustness of the conclusions derived from the statistical analyses and on their generalisation to the population of ALS patients to be treated with Rilutek.

Therefore an ad hoc experts group was called by the CPMP to discuss both statistical and clinical issues related to the interpretation of the clinical trials results. In preparation of this expert group meeting the Company was requested by the CPMP to answer some statistical questions on 20 October 1995 and the ad hoc working group met on 15 November 1995. A technical report summarising the status of methodological issues relating to efficacy of Rilutek was issued at request of the CPMP.

Study 216

This study was designed as multicentre, double blind, placebo-controlled, randomised, parallel group trial. 155 patients aged 19 to 75, were randomised to riluzole 100 mg/day (50 mg twice daily, 77 patients) or placebo (78 patients) and were followed-up for 12 to 21 months.

The ALS patients were stratified at entry into limb or bulbar onset form. Main exclusion criteria were: tracheotomy present or pending, dementia, vital capacity ratio <60%, significant renal or hepatic impairment. Patients who were pregnant, lactating or taking potentially hepatotoxic drugs were also excluded from the study.

The main efficacy endpoint was overall survival at one year. Secondary endpoints were changes from baseline in functional evaluation.

In the primary analysis, survival was significantly prolonged for patients who received riluzole as compared to patients who received placebo (survival rates were 55.8% versus 48.70 % for riluzole and placebo, respectively; p value = 0.116 Logrank test; p value = 0.047 Wilcoxon test; p value = 0.08 Cox model). All other analyses reached the significance level whatever the cut-off date or the statistical test was. The effect was more pronounced in patients with bulbar onset form (increase in survival time of about 8 months in comparison with placebo treated patients). The

enhanced efficacy amongst the bulbar stratum in comparison to the population with limbar onset was observed in the context of a sub-group analysis, and was not confirmed in later trials.

Overall, study 216 provided evidence of efficacy on survival: Nevertheless, no functional effect was evidenced.

Study 301

This study was designed as a multicentre, double blind, placebo-controlled, randomised, parallel group, dose ranging study.

Study 301 was a confirmatory trial comparing 3 doses of riluzole with placebo and was considerably larger than trial 216.
959 patients with ALS were randomised to one of four treatment groups: riluzole 50, 100, 200 mg/day, or placebo and were followed-up for 18 months. The ALS patients were stratified at entry into limb or bulbar onset form. Main exclusion criteria were: tracheotomy present or pending, dementia, vital capacity ratio < 60%, significant renal or hepatic impairment. Also patients pregnant, lactating or taking potentially hepatotoxic drugs were excluded.
The primary efficacy variable was survival with failure defined as death, tracheotomy or intubation at 18 months. Secondary efficacy parameters were changes from baseline in functional evaluations.

The comparison of 100 mg with placebo was defined in the protocol as the primary comparison.

In patients treated with riluzole 100 mg/day, survival was significantly higher compared to patients who received placebo (survival rates were 56.8% versus 50.4% for riluzole and placebo, respectively; p value = 0.05, Wilcoxon test. p value = 0.07 log-rank test; p value = 0.002 Cox model). No interaction of the treatment effect with the type of ALS was observed.

The effect of riluzole 50 mg/day was not statistically significant compared to placebo and the effect of 200 mg/day was essentially comparable to that of 100 mg/day.

No changes were observed from baseline in the functional evaluation.

At the CPMP request, the Company provided a full Cox model analysis for trial 301 including all pre-defined co-variables to see if these agreed with the results of their selected model presented in the study report. The key point of interest was the level of statistical significance attached to the treatment effects in the full Cox model. As was anticipated, the P-values were less extreme (50 mg p =0.082, 100 mg p =0.003, 200mg p =0.001) but the levels of significance attached to the higher dose levels remained high.

Concerns were discussed by the CPMP on any eventual implication of the interim analysis of survival in conjunction with the early stopping of the trial. The CPMP asked the Rapporteur to contact the Chairman of the data monitoring committee of trial 301 to clarify the procedures surrounding the interim analyses. He stated that the proceedings of the data monitoring committee had been entirely confidential and had not been revealed to the Company. No Company personnel were either on the committee or present at any of the meetings of the committee. The clinical trial data provided by the Company to the committee were not decoded nor analysed by the Company. They were provided in computer readable form only, code unbroken; the code was then broken and the data analysed at the University of Reading. No recommendations were made by the data monitoring committee to the Company as a result of the interim analysis of efficacy, and no results had been communicated. The decision of the Company to conclude the trial at the end of 1994 was not related to the work of his committee, but only to the recruitment of a sufficient number of patients.

There are therefore no implications for the levels of statistical significance achieved in this trial.

Additional analysis including patients who had a strict 18 months follow-up was performed at the request of the CPMP, to eliminate any aspects of data censoring, and also to eliminate potentially reduced efficacy during the early months of treatment. In fact the results of this analysis simply mirrored those of the main analysis.

A worst case analysis for the few patients lost to follow-up was provided and was appropriately carried out. Not surprisingly, levels of statistical significance were reduced. If the reliability of the results of the Cox analysis is accepted, then robustness to their patient losses is assured.

There is clear statistical evidence in study 301 of an effect of riluzole at 100 mg on survival. The results of the analysis using the Cox model are particularly convincing (p=0.002 in original report) and are not undermined by any of the queries raised. A further analysis by the Company used more robust methods of direct stratification by risk factors in order to confirm the results of the Cox model whilst making less assumptions. This confirmation was successful, and similar levels of significance were achieved.

The duration of follow-up was defined in the protocol. Crossing of survival curves on prolonged follow-up is possible in theory but not objectively founded. In no way could a longer follow-up change the initial 18 months part of the survival curves, nor could it change the difference of 3 months between the two medians of survival. Eventually the curves must cross, but this does not invalidate the survival benefit established in this study.

- A GCP inspection was conducted from June to September 1995 by the French Inspectorate. Four clinical Centers have been audited: in Canada (Centre CA 0029), in the United States (Centre US 0711) and in France (Centers FR 0252 and FR 0255). For the French and the U.S.A. centers a joint inspection with FDA has been performed. The inspection focused on the documentation concerning the determination of the status at the end of the 18 months follow-up or at the cut-off date. Documentation of the events deaths, intubation and tracheotomy, and follow-up of patients who had discontinued investigational drug treatment was reviewed.

  The compliance to treatment by patients was also reviewed.

  The conclusions of the French inspectorate are the following:

  > " The data reviewed in the course of the inspection for the abovementioned Clinical Centers can be considered authentic and credible, and their quality acceptable. The audit of the packaging and labeling of the drugs used in the EU sites did not identify any significant problem.

Study 302

This study was designed as a multicentre, double blind, placebo-controlled, randomised, parallel group trial and was a comparison of 100 mg with placebo in patients ineligible for trial 301, either with advanced disease or aged over 75 years or with vital capacity ratio less than 60%.

The planned size was 300 patients but only 168 patients were randomised to riluzole 100 mg/day or placebo and were followed up for 18 months: the protocolled power of the study was therefore not achieved in this study. In this population with decreased respiratory function, survival was not significantly higher in the riluzole group compared to the placebo group.

Methodologically, this was a properly conducted controlled trial. It was smaller than planned, and much smaller than study 301, but slightly larger than study 216.

There was some baseline imbalance in characteristics of patients related to prognosis but this was covered by the use of the Cox model. It therefore contributes valuable information, although the relevance of the patients included in this study to the potential target population is not entirely clear.

This study did not establish any effect of Rilutek on survival. In view of its relatively small sample size the confidence interval surrounding the finding of no difference is quite wide.

Metanalysis of the overall efficacy results

A meta analysis of studies 216, 301 and 302 was carried out by the company at request of the CPMP.

Despite the negativity of study 302, the overall statistical significance of the treatment effect is maintained (p=0.043 logrank test). The robustness of this finding is assured by the very high overall levels of statistical significance attached to the Cox model (p=0.0004). Therefore

statistically the results of study 302 could be chance findings within the context of an overall beneficial effect of Riluzole on survival.

The results of the analysis combining the three trials showed that the median survival benefit during a 18 month follow-up was approximately 2 months.

By-center analysis

Positive results were most consistent in France, Belgium and the UK. However, small numbers makes this analysis by-center, impossible to interpret statistically. The possible confounding with severity must also be born in mind. Statistically, the tests of interaction between the treatment effect and country were not significant, so that this pattern of result is consistent with chance.

Mortality as an end-point

If the end-point is taken as mortality only - excluding tracheotomy and intubation - the conclusions do not change. The rate of tracheotomy and/or intubation was very low in studies 216 and 301 indeed and most of these events were followed by death before reaching the cut-off date:

- study 216:
  6 tracheotomies in the placebo group: 3 deaths by the cut-off date
  5 tracheotomies in the riluzole group: 4 deaths by the cut-off date
- study 301:
  10 tracheotomies or intubation in the placebo group: 6 deaths by the cut-off date
  12 tracheotomies or intubation in the 100 mg riluzole group: 4 deaths by the cut-off date

Analysis by risk levels

An analysis separating patients in two risk levels: "high risk" and "low risk" was a posteriori performed, based on an initial risk index calculated for each patient. Efficacy on survival was only apparent in "high risk" patients of studies 216 and 301, thus evidencing that a benefit on survival can only be demonstrated in patients having reached a certain degree of severity of the disease.

Conclusions on efficacy

The original positive finding was the overall effect on the main efficacy criterion survival in study 216. This was then replicated in study 301 using the same dose of riluzole.

Study 302 conducted in patients at an advanced stage of the disease failed to establish an effect on survival. The meta-analysis of the three studies however remained positive.

The overall efficacy results appear not to vary substantially according to disease duration.

The failure to find any effect on functional end-points does not affect the reliability of the survival results but remains a concern even if a score on a specific functional scale has never been validated as a surrogate marker of survival.

There is no doubt that effects on functional end-points, if established, would help to support the survival results. If the levels of statistical significance attached to the survival effects were marginal, this might be an important point. However, the levels of statistical significance arising from the Cox model are sufficiently strong to stand on their own without the need for other support.

In all disease areas where survival data are important (e.g. AIDS, cancer) it is common practice to analyse survival data using all three statistical methods used in this application (logrank test, Wilcoxon test and Cox proportional hazard model). In general, with reasonably consistent results, an overall pattern of statistical significance in this group of tests is regarded as proof of efficacy, and statements in the protocol preferring one test over the others should not override sensible interpretation. The Cox model would be expected to achieve higher levels of statistical significance because of its greater sensitivity, and can be relied upon. The consistent outcome of the different analyses, together with the higher levels of statistical significance associated with the Cox model, is reassuring.

Clinical safety.

The following adverse reactions have been reported in patients enrolled in Phase III studies conducted in North America and Europe.

The listing that follows describes all the adverse events that occurred at a frequency of 1% or more among 794 ALS patients receiving riluzole and were greater than placebo by 1%, or were serious adverse events with frequency greater than placebo during the clinical studies.

The most frequent side-effects related to riluzole were asthenia, nausea and dizziness.

Other side-effects have been reported, although less commonly: abdominal pain, headache, diarrhea, pneumonia, vertigo, circumoral paresthesia, angioedema.

Riluzole appears to have potential hepatotoxic effects with cytolytic and cholestatic effects and may cause liver dysfunction. Elevations of alanine-aminotransferase (ALT) levels to more than 3 times the upper limit of the normal range (ULN) were observed in about 10 % of the patients treated with riluzole compared to 3.7 % in the placebo group; levels increased to more than 5 times the ULN in about 3% of the patients treated with riluzole compared to 2% of the placebo treated patients. The increases in ALT usually appeared within 3 months after the start of therapy with riluzole; they were usually transient and levels returned to below 2 times the ULN after 2 to 6 months while treatment was continued. These increases were rarely associated with jaundice. In patients with increases in ALT to more than 5 times the ULN, treatment was discontinued and the levels returned to less than 2 times the ULN within 2 to 4 months.

Anaphylactoid reaction and severe neutropenia have been reported, although exceptionally.

Among approximately 5000 patients given riluzole for ALS, there were three cases of marked neutropenia (absolute neutrophil count less than 500/mm^3), all seen within the first 2 months of riluzole treatment. In one case, neutrophil counts rose on continued treatment. In a second case, counts rose after therapy was stopped. A third case neutropenia was associated with marked anemia: reduction in hemoglobin levels was observed .

No adverse event on cognitive functions were observed.

No adverse effect on cardiovascular and respiratory function were observed.

Questions put to the Company:

Reservations on the clinical relevance of data observed with the treatment of ALS with Riluzole were discussed in depth by the Committee. These could be summarised as three main issues which were put to the Company during the hearing held at the CPMP meeting on 13 February 1996:

1. Can the lack of concordance between the benefit on survival and the lack of benefit on functional scales be explained?
2. Can causes of death other than ALS influence the results of the trials?
3. Are the trials robust enough to justify the conclusions drawn from the results?

The following responses were provided:

1. Lack of correlation in ALS between survival and different functional scales:

   The Manual Muscle Scale, the Norris scales (both used in the pivotal trials) and the Appel scoring system (not used in the trials conducted with riluzole) failed - according to the published literature - to show any firm correlation with survival in ALS. This lack of correlation was also found in the studies carried out with riluzole treatment. On these grounds, the functional scales are not yet validated as surrogate markers of survival in ALS.

2. As far as the second issue was concerned, it was clearly shown that the deaths due to ALS in the clinical studies submitted were at least 95% of all deaths. This finding was expected, being the natural evolution of the disease rapidly progressive to death. Any concern about the cause of death should be alleged by the design of the randomised, double-blind, controlled trials. The baseline prognostic factors were the same in the placebo and in the

Riluzole treatment arm and the overall crude mortality, in terms of time to death, (irrespective of the cause of death) was used as for the primary efficacy end-point.

3. As far as the robustness of the clinical studies is concerned there was substantial discussion. The results obtained showed a median increase in survival time. However, because of the lack of any change in the functional scales and in symptoms the clinical relevance of this results was considered debatable and ethical considerations had to be considered.

5. Conclusions

Riluzole has been demonstrated to extend survival in two studies conducted in patients with ALS, but not in a third trial. Survival was the main efficacy criteria and was considered as a strong outcome measure.

The failure to find any effect on functional end-points does not affect the reliability of the survival results.

The survival data obtained with Riluzole were analysed at several time-points to explore the robustness of the findings: the general consistency of the findings is of interest, rather than specific achievements of selected significance levels. The consistent outcome of significance levels achieved in the different analyses, together with the higher levels of statistical significance associated with the Cox model, is reassuring.

An effect on functional end-points, if established, would help to support the survival results: however up to date scores on functional scales are not validated as surrogate markers of survival in ALS.

The CPMP in their meeting on 14 February 1996 adopted by scientific consensus a positive opinion on Rilutek.

The Committee in recommending the granting of a marketing authorisation felt it was important to set out in the Summary of Product Characteristics the results of the clinical trials on which the authorisation was based. The Committee felt that this was particularly important because treatment with riluzole does not demonstrate a positive effect on functional symptoms of the disease whilst the magnitude of the effect on survival is modest. There are therefore remaining uncertainties on the product in the management of Amyotrophic Lateral Sclerosis.

The specialist physicians using riluzole will be fully aware of the data.

The therapeutic indication approved is the following:

"Riluzole is indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS).

Clinical trials have demonstrated that RILUTEK extends survival for patients with ALS.

Survival was defined as patients who were alive, not intubated for mechanical ventilation and tracheotomy-free.

There is no evidence that riluzole exerts a therapeutic effect on motor function, lung function, fasciculations, muscle strength and motor symptoms. Riluzole has not been shown to be effective in the late stages of ALS.

Safety and efficacy of riluzole has only been studied in ALS. Therefore, riluzole should not be used in any other form of motor neuron disease."

Further information on clinical trials:

In a trial, 155 patients were randomised to riluzole 100 mg/day (50 mg twice daily) or placebo and were followed-up for 12 to 21 months. Survival, as defined in the second paragraph of section 4.1., was significantly extended for patients who received riluzole as compared to patients who received placebo. The median survival time was 17.7 months versus 14.9 months for riluzole and placebo, respectively.

In a dose-ranging trial, 959 patients with ALS were randomised to one of four treatment groups: riluzole 50, 100, 200 mg/day, or placebo and were followed-up for 18 months. In patients treated with riluzole 100 mg/day, survival was significantly higher compared to patients who received placebo. The effect of riluzole 50 mg/day was not statistically significant compared to placebo and the effect of 200 mg/day was essentially comparable to that of 100 mg/day. The median survival time approached 16.5 months versus 13.5 months for riluzole 100 mg/day and placebo, respectively.

In a parallel group study designed to assess the efficacy and safety of riluzole in patients at a late stage of the disease, survival time and motor function under riluzole did not differ significantly from that of placebo. In this study the majority of patients had a vital capacity ratio less than 60%."

IV ANNEXES

1. CPMP OPINION (CPMP/132/96)

CPMP/132/96
Procedure No. EMEA/H/C/109/00/00

OPINION OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS ON THE GRANTING OF A MARKETING AUTHORISATION

Name of the product:	RILUTEK
International Non-proprietary Name:	Riluzole
Strength:	50 mg
Pharmaceutical form:	Coated tablet
Route of administration:	Oral use
Package size:	Blister containing 56 tablets

Basis for opinion

Pursuant to Article 6 of Council Regulation No. 2309/93 the Company Rhône-Poulenc Rorer submitted to the EMEA on 3 July 1995 an application concerning the above mentioned product which falls within the scope of Part B of the Annex to Council Regulation (EEC) No. 2309/93 of 22 July 93.

Written explanation was provided by the company on 22 December 1995.
Oral explanations were given on 13 February 1996.

Opinion

1. The Committee, having considered the application as stated in the appended assessment report, recommends the granting of a marketing authorisation, in accordance with the Summary of Product Characteristics in Annex I.

2. Manufacturing Authorisation and conditions of the Marketing Authorisation, including conditions or restrictions regarding supply and use are stated in Annex II.

3. Labelling and User Package Leaflet are presented in Annex III.

The Committee in recommending the grant of a marketing authorisation felt it was important to set out in the Summary of Product Characteristics the results of the clinical trials on which the authorisation was based. This means that the specialist physicians using riluzole will be fully aware of the data. The Committee felt that this was particularly important because treatment with riluzole does not demonstrate a positive effect on functional symptoms of the disease whilst the magnitude of the effect on survival is modest. There are therefore remaining uncertainties on the product in the management of Amyotrophic Lateral Sclerosis.

The present opinion is forwarded to the Commission, to Member States and to the applicant together with its annexes and appendices.

London, 14 February 1996

Prof. J.M. Alexandre,
Chairman, on behalf of the Committee

2. SUMMARY OF PRODUCT CHARACTERISTICS
updated on 17 October 1997

1. NAME OF THE MEDICINAL PRODUCT

RILUTEK

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: riluzole 50 mg

3. PHARMACEUTICAL FORM

Capsule-shaped, white, film-coated tablets for oral use. The tablets are engraved with « RPR 202 » on one side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Riluzole is indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS).

Clinical trials have demonstrated that RILUTEK extends survival for patients with ALS.
Survival was defined as patients who were alive, not intubated for mechanical ventilation and tracheotomy-free.

There is no evidence that riluzole exerts a therapeutic effect on motor function, lung function, fasciculations, muscle strength and motor symptoms. Riluzole has not been shown to be effective in the late stages of ALS.

Safety and efficacy of riluzole has only been studied in ALS. Therefore, riluzole should not be used in any other form of motor neurone disease.

Further information on clinical trials:

In a trial, 155 patients were randomised to riluzole 100 mg/day (50 mg twice daily) or placebo and were followed-up for 12 to 21 months. Survival, as defined in the second paragraph of section 4.1., was significantly extended for patients who received riluzole as compared to patients who received placebo. The median survival time was 17.7 months versus 14.9 months for riluzole and placebo, respectively.

In a dose-ranging trial, 959 patients with ALS were randomised to one of four treatment groups: riluzole 50, 100, 200 mg/day, or placebo and were followed-up for 18 months. In patients treated with riluzole 100 mg/day, survival was significantly higher compared to patients who received placebo. The effect of riluzole 50 mg/day was not statistically significant compared to placebo and the effect of 200 mg/day was essentially comparable to that of 100 mg/day. The median survival time approached 16.5 months versus 13.5 months for riluzole 100 mg/day and placebo, respectively.

In a parallel group study designed to assess the efficacy and safety of riluzole in patients at a late stage of the disease, survival time and motor function under riluzole did not differ significantly from that of placebo. In this study the majority of patients had a vital capacity less than 60%.

4.2 Posology and method of administration

The recommended daily dose in adults or elderly is 100 mg (50 mg every 12 hours).
No significant increased benefit can be expected from higher daily doses.
Treatment with riluzole should only be initiated by specialist physicians with experience in the management of motor neurone diseases.

Special populations:

Children: RILUTEK is not recommended for use in children, as the safety and effectiveness of riluzole in any neurodegenerative process occurring in children or adolescents have not been established. (see « SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE »).

Patients with Impaired Renal Function: RILUTEK is not recommended for use in patients with impaired renal function, as studies at repeated doses have not been conducted in this population (see « SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE »).

Elderly: Based on pharmacokinetic data, there are no special instructions for the use of RILUTEK in this population.

Patients with Impaired Hepatic Function: (see « CONTRAINDICATIONS », « SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE » and « PHARMACOKINETIC PROPERTIES »).

4.3 Contraindications

Patients who have a history of severe hypersensitivity reactions to riluzole or any of the tablet components.

Patients who have hepatic disease or who have baseline transaminases greater than 3 times the upper limit of normal.

Patients who are pregnant or lactating.

4.4 Special warnings and special precautions for use

Liver impairment

Riluzole should be prescribed with care in patients with a history of abnormal liver function, or in patients with slightly elevated serum transaminases (ALT/SGPT; AST/SGOT up to 3 times ULN), bilirubin and/or gamma-glutamyl transferase (GGT) levels. Baseline elevations of several liver function tests (especially elevated bilirubin) should preclude the use of riluzole. (see « UNDESIRABLE EFFECTS »).

It is recommended that serum transaminases, including ALT, be measured before and during therapy with riluzole. ALT should be measured every month during the first 3 months of treatment, every 3 months during the remainder of the first year, and periodically thereafter. ALT levels should be measured more frequently in patients who develop elevated ALT levels.

Riluzole should be discontinued if the ALT levels increase to five times the ULN. There is no experience with dose reduction or rechallenge in patients who have developed an increase of ALT to 5 times ULN. Readministration of riluzole to patients in this situation cannot be recommended.

Neutropenia:
Patients should be warned to report any febrile illness to their physicians. The report of a febrile illness should prompt physicians to check white blood cell counts and to discontinue riluzole in case of neutropenia. (see « UNDESIRABLE EFFECTS »).

Children
The safety and effectiveness of riluzole in any neurodegenerative process occurring in children or adolescents have not been studied. (see « POSOLOGY AND METHOD OF ADMINISTRATION »)

Patients with Impaired Renal Function
Studies at repeated doses have not been conducted in this population (see « POSOLOGY AND METHOD OF ADMINISTRATION »).

4.5 Interaction with other medicines and other forms of Interaction

There have been no clinical studies to evaluate the interactions of riluzole with other drugs.

In vitro studies using human liver microsomal preparations suggest that CYP 1A2 is the principal isozyme involved in the initial oxidative metabolism of riluzole. Inhibitors of CYP 1A2 (e.g. caffeine, diclofenac, diazepam, nicergoline, clomipramine, imipramine, fluvoxamine, phenacetin, theophylline, amitriptyline and quinolones) could potentially decrease the rate of riluzole elimination, while inducers of CYP 1A2 (e.g. cigarette smoke, charcoal-broiled food, rifampicin and omeprazole) could increase the rate of riluzole elimination.

4.6 Pregnancy and lactation

Pregnancy:
In the pregnant rat, the transfer of ^{14}C- riluzole across the placenta to the foetus has been detected. In rats, riluzole decreased the pregnancy rate and the number of implantations at exposure levels at least 2 times higher than the systemic exposure of humans given clinical therapy. No malformations were seen in animal reproductive studies.
Clinical experience with riluzole in pregnant women is lacking. Riluzole must not be used in pregnant women.

Lactation:
In lactating rats, ^{14}C-riluzole was detected in milk. It is not known whether riluzole is excreted in human milk. Riluzole must not be used in lactating women.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness or vertigo, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

The following adverse reactions have been reported in patients enrolled in Phase III studies conducted in Europe and North America.

The most frequent side-effects related to riluzole were asthenia, nausea and elevations in liver function tests.
Elevations of alanine-aminotransferase (ALT) levels to more than 3 times the upper limit of the normal range (ULN) were observed in about 11 % of the patients treated with riluzole compared to 4.2 % in the placebo group; levels increased to more than 5 times the ULN in 3.8% of the patients treated with riluzole compared to 1.7 % of the placebo treated patients. The increases in ALT usually appeared within 3 months after the start of therapy with riluzole; they were usually transient and levels returned to below 2 times the ULN after 2 to 6 months while treatment was continued. These increases were rarely associated with jaundice. In patients with increases in ALT to more than 5 times the ULN, treatment was discontinued and the levels returned to less than 2 times the ULN within 2 to 4 months. (see « SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE »).

The listing that follows describes all the adverse events that occurred at a frequency of 1% or more among ALS patients receiving riluzole 100 mg/day and were greater than placebo by 1%, or were serious adverse events with frequency greater than placebo.

Adverse Events Occurring in Placebo-Controlled Clinical Trials Percentage of patients reporting events*		
Adverse Event*	**Riluzole 100 mg/day (N=395)**	**Placebo (N=406)**
Asthenia	17.5	11.3
Nausea	14.2	9.1
Headache	6.8	5.7
Abdominal pain	5.1	3.7
Pain	4.8	2.0
Vomiting	3.8	1.5
Dizziness	3.3	2.2
Tachycardia	3.0	1.5
Somnolence	2.0	1.0
Circumoral paresthesia	1.3	0.0
* Where riluzole incidence is greater than placebo by 1%.		

Anaphylactoid reaction and angioedema have been reported exceptionally.

Among approximately 5000 patients given riluzole for ALS, there were three cases of marked neutropenia (absolute neutrophil count less than 500/mm^3), all seen within the first 2 months of riluzole treatment. In one case, neutrophil counts rose on continued treatment. In a second case, counts rose after therapy was stopped. A third case was associated with marked anemia (see « SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE »).

4.9 Overdose

There have been no reports of overdose with riluzole; no specific treatment information or antidote are available. In case of overdosage, treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Pharmaco-therapeutic group: other nervous system drugs, ATC code NO7X.

5.1 Pharmacodynamic properties

Although the pathogenesis of ALS is not completely elucidated, it is suggested that glutamate (the primary excitatory neurotransmitter in the central nervous system) plays a role for cell death in the disease.

Riluzole is proposed to act by inhibiting glutamate processes. The mode of action is unclear.

5.2 Pharmacokinetic properties

The pharmacokinetics of riluzole have been evaluated in healthy male volunteers after single oral administration of 25 to 300 mg and after multiple-dose oral administration of 25 to 100 mg bid. Plasma levels increase linearly with the dose and the pharmacokinetic profile is dose-independent. With multiple dose administration (10 day-treatment at 50 mg riluzole bid), unchanged riluzole accumulates in plasma by about 2 fold and steady-state is reached in less than 5 days.

ABSORPTION
Riluzole is rapidly absorbed after oral administration with maximal plasma concentrations occurring within 60 to 90 minutes (C_{max} = 173 ± 72 (SD) ng/ml). About 90% of the dose is absorbed and the absolute bioavailability is 60 ± 18%.

The rate and extent of absorption is reduced when riluzole is administered with high-fat meals (decrease in C_{max} of 44%, decrease in AUC of 17%).

DISTRIBUTION
Riluzole is extensively distributed throughout the body and has been shown to cross the blood brain barrier. The volume of distribution of riluzole is about 245 ± 69 l (3.4 l/kg). Riluzole is about 97% protein bound and it binds mainly to serum albumin and to lipoproteins.

Metabolism
Unchanged riluzole is the main component in plasma and is extensively metabolised by cytochrome P450 and subsequent glucuronidation. In vitro studies using human liver preparations demonstrated that cytochrome P450 1A2 is the principal isoenzyme involved in the metabolism of riluzole. The metabolites identified in urine are 3 phenolic derivatives, one ureido-derivative and unchanged riluzole.

The identified and non-conjugated metabolites do not contribute to the pharmacodynamic profile of riluzole in animals and therefore have not been investigated in humans.

ELIMINATION
The elimination half-life ranges from 9 to 15 hours. Riluzole is eliminated mainly in the urine. The overall urinary excretion accounts for about 90% of the dose. Glucuronides accounted for more than 85% of the metabolites in the urine. Only 2% of a riluzole dose was recovered in the urine as unchanged drug.

Special populations

Patients with Impaired Renal Function: There is no significant difference in pharmacokinetic parameters between patients with moderate or severe chronic renal insufficiency (creatinine clearance between 10 and 50 $ml.min^{-1}$) and healthy volunteers after a single oral dose of 50 mg riluzole.

Elderly: The pharmacokinetic parameters of riluzole after multiple dose administration (4.5 days of treatment at 50 mg riluzole bid) are not affected in the elderly (> 70 years).

Patients with Impaired Hepatic Function: The AUC of riluzole after a single oral dose of 50 mg increases by about 1.7 fold in patients with mild chronic liver insufficiency and by about 3 fold in patients with moderate chronic liver insufficiency.

5.3 Preclinical safety data

Long-term studies to determine the carcinogenic potential of riluzole have not yet been completed.

Conventional genotoxicity assays in vitro, utilising rat liver S9 fraction to model metabolism, gave no evidence of genotoxic potential for riluzole. In vivo assays in rat and mouse also gave no indication of chromosomal damage. There remains the possibility that these models did not generate all metabolites relevant to humans, particularly since no metabolic characterisation of the S9 fraction was conducted.
Reductions in red blood cell parameters and/or alterations in liver parameters were noted inconsistently in subacute and chronic toxicity studies in rats and monkeys. In dogs, haemolytic anaemia was observed.

In a single toxicity study, the absence of corpora lutea was noted at a higher incidence in the ovary of treated compared to control female rats. This isolated finding was not noted in any other study or species.

All these findings were noted at doses which were 2-10 times higher than the human dose of 100 mg/day.

Fertility studies in rats revealed slight impairment of reproductive performance and fertility at doses of 15 mg/kg/day (which is higher than the therapeutic dose), probably due to sedation and lethargy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

core: dibasic calcium phosphate, anhydrous; micro crystalline cellulose; colloidal silica, anhydrous; magnesium stearate; cross linked carboxymethylcellulose sodium (croscarmellose sodium);

coating: hydroxypropylmethyl cellulose; Macrogol 6000 and titanium dioxide (E171).

6.2 Incompatibilities

None known.

6.3 Shelf-life

The shelf-life is 24 months.

6.4 Special precautions for storage

RILUTEK must be kept out of the reach of children.

6.5 Nature and contents of container

RILUTEK coated tablets are packaged in opaque PVC/Aluminium blister packs.
Each package contains 4 blister cards of 14 tablets each.

6.6 Instructions for use/handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Rhône-Poulenc Rorer S.A.
20 avenue Raymond Aron
92165 Antony Cedex
France

8. MARKETING AUTHORISATION NUMBER

EU/1/96/010/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 June 1996

10. DATE OF (PARTIAL) REVISION OF THE TEXT

3. LABELLING AND PACKAGE LEAFLET

3.1 LABELLING

CARTON LABEL FOR RILUTEK (riluzole)

Face 1

RILUTEK
riluzole

50 mg

For oral use

56 coated tablets

Marketing Authorisation Holder:
Rhône-Poulenc Rorer S.A.
20 avenue Raymond Aron
92165 Antony Cedex
France

Face 2

RILUTEK
riluzole

56 coated tablets

Composition:

- riluzole..... 50 mg
- excipients..... q.s 1 coated tablet
- Colouring agent E 171

Authorisation number:

CARTON LABEL FOR RILUTEK (riluzole)

Face 3

RILUTEK
riluzole

50 mg

For oral use

See accompanying instructions for use

Keep out of the reach of children

Medicinal product subject to medical prescription

Face 4

RILUTEK
riluzole

50 mg

CARTON LABEL FOR RILUTEK (riluzole)

Face 5

RILUTEK
riluzole

50 mg

For oral use

56 coated tablets

RHÔNE-POULENC RORER

Face 6

Batch Number:

Expiry date:

BLISTER TEXT FOR RILUTEK (riluzole)

RILUTEK
riluzole

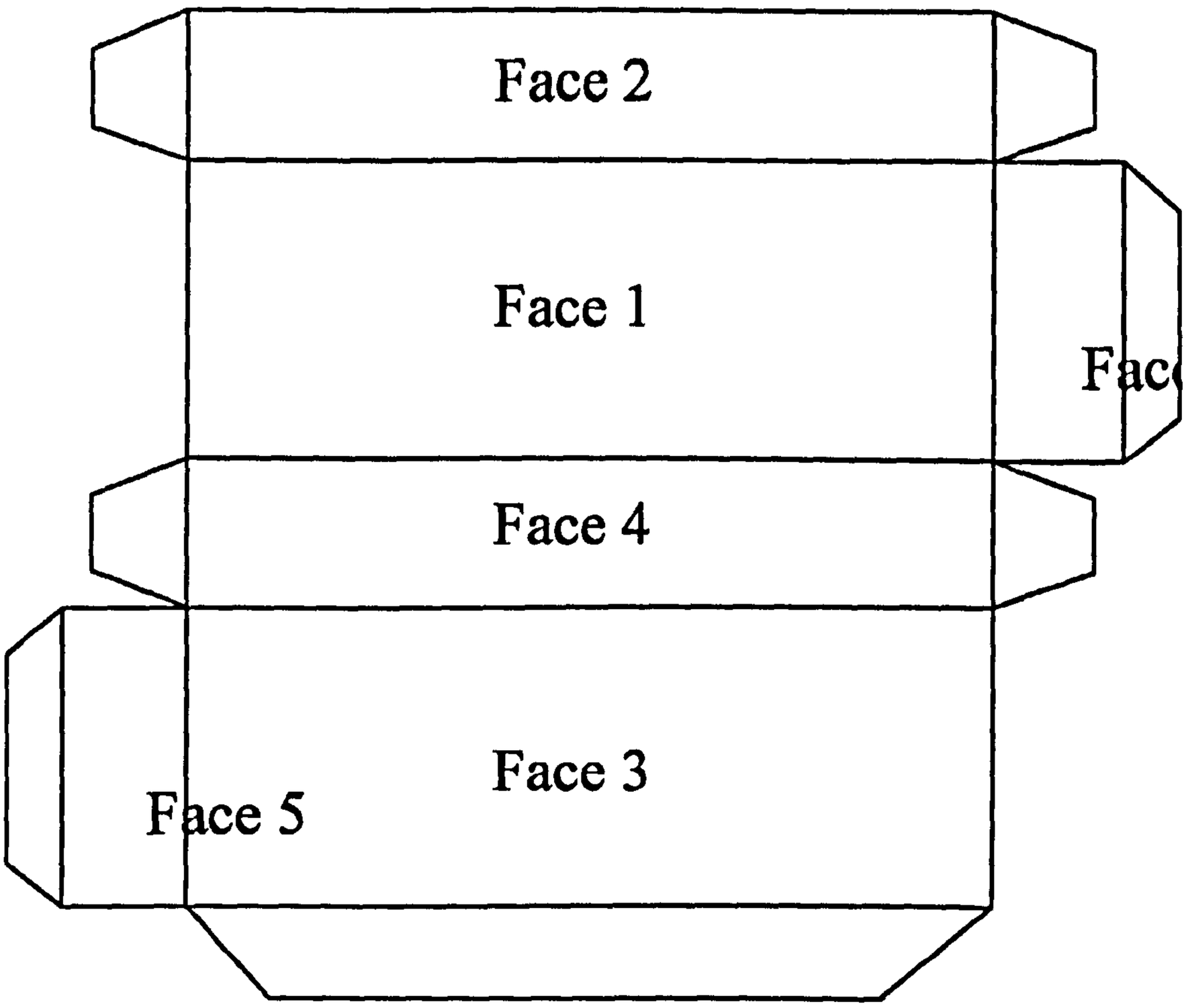
50 mg

Batch Number

Expiry date

RHÔNE-POULENC RORER

CARTON LABEL FOR RILUTEK (riluzole)



3.2 PACKAGE LEAFLET
updated on 17 October 1997

Your doctor has prescribed RILUTEK (riluzole) for you. Your doctor will discuss and explain to you the benefits and risks with RILUTEK.
Please read this leaflet carefully, it is a summary of the information about RILUTEK that could be important for you.

If you have any questions, or are not sure about anything to do with your treatment, ask your doctor or pharmacist for more information.

RILUTEK must not be given to anyone other than the person for whom it was prescribed.

Keep this leaflet in a safe place, you may want to refer to it again.

1. WHAT ARE THE GENERAL CHARACTERISTICS OF RILUTEK?

WHAT IS RILUTEK?

The active ingredient in RILUTEK is riluzole. RILUTEK is a capsule-shaped white, film-coated tablets containing 50 mg riluzole engraved with « RPR 202 » on one side of the tablet.

Each tablet contains the following inactive ingredients:
core: dibasic calcium phosphate, anhydrous; micro crystalline cellulose; colloidal silica, anhydrous; magnesium stearate; cross linked carboxymethylcellulose sodium (croscarmellose sodium);
coating: hydroxypropylmethyl cellulose; Macrogol 6000 and titanium dioxide (E171).

RILUTEK is available in a package of 4 blister cards of 14 tablets each for oral administration.

WHO IS THE MARKETING AUTHORISATION HOLDER FOR RILUTEK?

The Marketing Authorisation Holder is

Rhône-Poulenc Rorer S.A.
20 avenue Raymond Aron.
92165 Antony Cedex
France

WHO MANUFACTURES RILUTEK?

The product is manufactured by:

Rhône-Poulenc Rorer Pharmaceuticals Limited,
Lisbunny Industrial Estate,
Nenagh,
Co. Tipperary,
Republic of Ireland.

2. WHAT IS RILUTEK FOR?

RILUTEK has been prescribed by your doctor for a disease of the nervous system affecting your muscle strength called amyotrophic lateral sclerosis. Your doctor may give you further information about why this medicine has been prescribed for you.

3. WHEN WILL YOU NOT USE RILUTEK?

RILUTEK must NOT be used:

- if you have had any allergic reaction to it or any of the tablet components,
- if you have a liver disease or abnormal elevations of some enzymes of the liver (transaminases),
- if you are pregnant or breast-feeding.

4. ARE THERE ANY SPECIAL WARNINGS AND PRECAUTIONS FOR THE USE OF RILUTEK?

You should tell your physician if you have ever had liver disease because RILUTEK may not be suitable for you.

Elevations of blood levels of some enzymes of the liver (transaminases) may occur. Your physician will do regular blood tests to follow this during treatment, and will take the necessary measures should increases occur.

Decreases in the number of white blood cells (which are important in fighting infections) may occur. In case you experience any fever (increase in temperature), you must call your doctor immediately.

You should tell your physician if you have a kidney disease.

CAN YOU USE RILUTEK DURING PREGNANCY OR WHILE BREAST-FEEDING?

If you are pregnant or think you are, you must NOT use RILUTEK.
You must NOT breast-feed infants while taking RILUTEK tablets.

IF YOU THINK YOU ARE PREGNANT OR COULD BECOME PREGNANT, DISCUSS THIS MATTER WITH YOUR DOCTOR. ALSO DISCUSS WITH YOUR DOCTOR IF YOU INTEND TO BREAST-FEED.

CAN YOU USE RILUTEK TOGETHER WITH OTHER MEDICINES?

If you are taking any medicine, tell your doctor BEFORE you use RILUTEK.
If you have to go to a doctor, dentist or hospital for any reason, tell them that you are taking RILUTEK.

CAN YOU DRIVE OR USE MACHINES?

If you have vertigo or feel dizzy when you take RILUTEK, you should NOT drive a vehicle or use machines.

5. HOW SHOULD YOU TAKE RILUTEK?

WHAT IS THE DOSAGE OF RILUTEK?

The recommended dose that you take is one tablet of RILUTEK twice a day.
You should take this medicine by the oral route on a regular basis and at the same time of the day (e.g. in the morning and evening) each day.

If you miss a dose of this medicine, take the next tablet as originally planned.

WHAT CAN HAPPEN IF YOU TAKE MORE RILUTEK TABLETS THAN PRESCRIBED BY YOUR PHYSICIAN?

There is no benefit in increasing the dose above 2 tablets per day. However, you may encounter more side-effects.

6. DOES RILUTEK HAVE ANY SIDE EFFECTS ?

A medicine may occasionally have some unwanted effects (known as side effects) and your doctor will discuss these with you..

The most common side effects of RILUTEK that you may encounter are tiredness, stomach upset, and elevations of blood levels of some enzymes of the liver (transaminases) (see ARE THEY ANY SPECIAL PRECAUTIONS FOR THE USE OF RILUTEK)?

The other side effects of RILUTEK are less common: stomach ache, headache, vomiting, increase in heart beat, dizziness, sleepiness or allergic reactions.

Decreases in the number of white blood cells (which are important in fighting infections) may occur [(see ARE THEY ANY SPECIAL PRECAUTIONS FOR THE USE OF RILUTEK)?]

RILUTEK may have other unwanted effects which have not been described here. IF YOU NOTICE ANY CHANGE IN YOUR HEALTH WHILE TAKING RILUTEK, TELL YOUR DOCTOR OR PHARMACIST.

7. HOW SHOULD RILUTEK BE KEPT?

RILUTEK MUST BE KEPT OUT OF REACH OF CHILDREN.

Do not use this medicine past its expiry date. This date is located on the box.

8. WHEN WAS THIS PATIENT LEAFLET PREPARED?

RILUTEK

Hvis Du ønsker yderligere oplysninger om dette lægemiddel, bedes Du kontakte den lokale filial af Rhône-Poulenc Rorer S.A.

Voor informatie over dit geneesmiddel kunt u contact opnemen met de lokale vertegenwoordiger van Rhône-Poulenc Rorer S.A.

For any information about this medicinal product, please contact your local representative of Rhône-Poulenc Rorer S.A.

Saadaksesi lisätietoja tästä lääkevalmisteesta ota yhteyttä Rhône-Poulenc Rorer S.A.:n paikalliseen edustajaan.

Pour toute information concernant ce médicament, merci de contacter le représentant dans votre pays de Rhône-Poulenc Rorer S.A.

Bei Anfragen zu diesem Arzneimittel wenden Sie sich bitte an Ihre Rhône-Poulenc Rorer S.A. Landesvertretung.

Για οποιαδήποτε πληροφορία σχετικά με αυτό το φαρμακευτικό προϊόν, παρακαλείσθε όπως επικοινωνήσετε με τον κατά τόπους αντιπρόσωπο της Rhône-Poulenc Rorer S.A.

Per ogni informazione su questa specialità medicinale, si prega di contattare il vostro rappresentante locale della Rhône-Poulenc Rorer S.A.

Para qualquer informação sobre este medicamento é favor contactar o seu representante local da Rhône-Poulenc Rorer S.A.

Por favor, para cualquier información sobre este medicamento contacte con su representante local de Rhône-Poulenc Rorer S.A.

För vidare information om detta läkemedel, kontakta Ditt lokala ombud för Rhône-Poulenc Rorer S.A.

Belgique / Belgien / België
Rhône-Poulenc Rorer SA/NV
Boulevard Sylvain Dupuislaan 243 b.3
Bruxelles 1070 Brussel
☎ (32)(2) 529 4611

Danmark
Rhône-Poulenc Rorer A/S
Kongevejen 100
2840 Holte
☎ (45) 45 47 70 00

Deutschland
Rhône-Poulenc Rorer GmbH
Nattermannallee 1
50829 Köln
☎ (49) (0) 221 509 01

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Rhône-Poulenc Rorer S.A.
Avenida de Leganés, 62
Apartado 196
28925 Alcorcón (Madrid)
☎ (34) (1) 685 82 00

France
Spécia
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92545 Montrouge Cedex
☎ (33) (0) 1 55 71 55 71

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1185 XE Amstelveen
☎ (31) (020) 547 39 22

Österreich
Rhône-Poulenc Rorer Pharmazeutika
Handels GmbH
Grinzinger Allee 18-20
A-1190 Wien
☎ (43-1) (0222) 318 40 60-0

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Rhône-Poulenc Rorer Lda.
Centro Empresarial Torres de Lisboa
Rua Tomás da Fonseca, Torre A, r/c B
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☎ (351) (1) 721 55 01

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RPR House
50 Kings Hill Avenue,
Kings Hill,
West Malling,
ME19 4AH
☎ (44) (0) 990 239 604

Appendix XXVI

Advertising Prosecutions reported in MAIL (1973 - 1997)

"A Person" Ealing Magistrates' Court 1981 [MAIL33]	"Advertising medicinal products for purposes prohibited by Regulations" 3 offences: Costs:	 £300 £50
"A Person" Billericay Magistrates' Court 12 March 1982 [MAIL34]	The Medicines (Labelling and Advertising to the Public) Regulations 1978 3 offences: Costs: [The defendant asked for a further 50 advertising offences to be taken into consideration.]	 £150 £250
"A Company and Two Directors" Dover Magistrates' Court 17 January 1986 [MAIL47]	Regulation 4 of the Medicines (Labelling and Advertising to the Public) Regulations 1978 1 offence: Costs: [*The fine also covered the supply of prescription only medicines without a doctor's prescription and the assembly of medicinal products without a manufacturer's licence.]	 Fined £1,700* £100
"A Company and its Medical Director" Central Criminal Court 19 December 1986 [MAIL49]	Section 93 of the Medicines Act 1968 8 offences: Costs:	 Company fined £20,000 Director fined £1,000 £93,800
"A Person" Willesden Magistrates' Court 8 July 1987 [MAIL51]	"Advertising irregularities" 1 offence: Costs:	 2 year conditional discharge £100
Kalecross Limited Hendon Magistrates' Court 30 November 1987 [MAIL53]	"An advertising offence" 1 offence: Costs: [*The fine also covered 3 offences involving the importation and supply of a medicinal product without a product licence and assembling a medicinal product without a manufacturer's licence.]	 Fined £3,400* £100
Fetouris International Limited Uxbridge Magistrates" Court 15 February 1988 [MAIL54]	"A breach of the Advertising Regulations" 1 offence Costs: [*The fine also covered two charges involving the importation and sale of a medicinal product without a product licence.]	 Fined £1,100* £150

Anne Summers (Sales) Ltd. and Gold Star Publications Ltd. Godstone Magistrates' Court 16 August 1988 [MAIL 57]	"Advertising offences" ?offences: Each company fined £250 Costs: n/s
X-Dent Ltd. Great Yarmouth Magistrates' Court 26 February 1990 [MAIL 63]	Regulation 2 of the Medicines (Advertising to the Medical and Dental Practitioners) Regulations 1978 ?offences: Fined £1200* Costs: £300 [*The fine also covered the charge of supplying prescription only medicines to an unauthorised person contrary to Regulation 5(1) of the Medicines (Sale and Supply)(Miscellaneous Provisions) Regulations 1978.]
Eric Clark Norwich Magistrates' Court 15 March 1990 [MAIL 63]	Regulation 3 of the Medicines (Labelling and Advertising to the Public) Regulations 1978 1 offence: Fined £150* Costs: £100 [*The fine also covered a charge of supplying anabolic steroids by mail order without a prescription.]
John Vassiliou of Hair and Beauty Trading Co. Enfield Magistrates' Court 22 May 1991 [MAIL 68]	Regulations 3 and 12 of the Medicines (Labelling and Advertising to the Public) Regulations 1978 3 offences: Fined £650* Costs: £50 [*The fine also covered the sale of a prescription only medicine (Minoxidil) to the general public, contrary to sections 58(2) and 67(2) of the Medicines Act 1968.]
Edgbaston Medical Group Birmingham Magistrates' Court 3 June 1991 [MAIL 68]	Regulations 3 and 12 of the Medicines (Labelling and Advertising to the Public) Regulations 1978 6 offences: Fined £3000 Costs: £500 [Involved Minoxidil]
Transform Partnership (Cosmetic Surgery Limited) Doncaster Crown Court 21 June 1991 [MAIL 69]	Regulations 3 and 12 of the Medicines (Labelling and Advertising to the Public) Regulations 1978 3 offences: Fined £1000 Costs: £1000 [Involved Minoxidil]
Norman Abrahams of Bioteq Limited West London Magistrates' Court 10 July 1991 [MAIL 69]	Regulations 3 and 12 of the Medicines (Labelling and Advertising to the Public) Regulations 1978 3 offences: Conditional discharge of 12 months on each charge Costs: £300 [Involved Minoxidil]
John A. Woodham of Bioteq Limited Swindon Magistrates' Court 30 July 1991 [MAIL 69]	Regulations 3 and 12 of the Medicines (Labelling and Advertising to the Public) Regulations 1978 3 offences: Conditional discharge of 12 months on each charge Costs: £300 [Involved Minoxidil]

N.S. Hair Treatment Clinic (UK) West London Magistrates' Court 10 July 1991 [MAIL 69]	Regulations 3 and 12 of the Medicines (Labelling and Advertising to the Public) Regulations 1978 2 offences: £100 Costs: £300 [Involved Minoxidil]
Regrow Hair Clinic (UK) Limited Hendon Magistrates' Court 25 September 1991 [MAIL 69]	Regulations 3 and 12 of the Medicines (Labelling and Advertising to the Public) Regulations 1978 3 offences: £750 Costs: £100 [Involved Minoxidil]
Glen James Wicks De La Ronde-Wilton trading as The National Hair Clinic Cardiff Magistrates' Court 11 November [MAIL 69]	Regulations 3 and 12 of the Medicines (Labelling and Advertising to the Public) Regulations 1978 2 offences: Fined £400 Costs: £200 [Involved Minoxidil]
Andrew Thomas Harrison and VoluMed (Manchester) Ltd. Manchester Magistrates' Court 25 February 1992 [MAIL 72]	Regulations 3 and 12 of the Medicines (Labelling and Advertising to the Public) Regulations 1978 2 offences: Harrison fined £450 Company fined £450 Costs: £160 [Involved Minoxidil]
Elizabeth Marsh trading as the Bio-Medical Care Clinic Isleworth Crown Court 29 March 1993 [MAIL 77]	Sections 93(1) and 93 (9) of the Medicines Act 1968 1 offence: Fine unspecified [Involved the issue of a misleading booklet which claimed that a substance called C116 could cure cancer.]
Elizabeth Anafo Camberwell Magistrates' Court 13/14 April 1993 [MAIL 77]	Regulation 4 and 12 of the Medicines (Labelling and Advertising to the Public) Regulations 1978 ?offences: £750* Costs: £250 [*The fine also covered the supply of unlicensed herbal products contrary to sections 7, 45, 58(2) and 67(2) of the Medicines Act 1968 and the Medicines (Products other than Veterinary Drugs) Order 1983.]
Robert Dickson and Bernard Booth Doncaster Crown Court Date unspecified [MAIL 93]	Regulations 3 and 12 of the Medicines (Labelling and Advertising to the Public) Regulations 1978 ?offences Both given conditional discharges Costs: £500 [The charges involved Tretinoin, a vitamin A derivative. Also included a breach of Section 52 of the Medicines Act]
DarrenGreen Wolverhampton Combined Court Centre 21 November 1995 [MAIL 93]	"Advertising offence" 1 offence 6 months Costs: £1000 [Involved the sale of anabolic steroids and methadone by mail order]

Mapleleaf Holdings Ltd Manchester Crown Court 17 March 1997 [MAIL 101]	Section 95 of the Medicines Act and Regulation 12 of the Medicines (Labelling and Advertising to the Public) Regulations 2 offences: £1500 Costs: £15038 [Involved the marketing of "Double Strength Oestrogen Hormone Breast Cream", Anti-Androgen Hormone Body Hair Retardant", "Oestrogen Breast Development Cream" and "Hormone Beard Retardant" to transsexuals. Other charges included the illegal manufacture or assembly of medicinal products, sale of products not on the general sale list and sale of prescription only medicinal products. Total fine was £6,750]

Appendix XXVII

Analysis of Breaches of the Code of Practice for the Pharmaceutical Industry (1983 - 1996)

Table A Medicinal products in breach of the Code of Practice (1983 - 1996)

One case:
Accupro; Acepril; Actisite; Adizem SR; Aerocrom Syncroner; Alec; Arelix; Astemizole; Aurum; Bactigras; Beclazone; Beclomethasone Dipropionate; Benzamycin; Blood products; Breath-actuated inhaler device; Brufen; Brufen Retard; Camcolit 250; Camcolit 400; Capasal; Cedax; Cefizox; Ceporex; Chymodiactin; Cipramil; Ciproxin; Cisplatin; Clexane; Clinitar; Cocois; Co-danhramer; Colifoam; Colpermin; Coracten; Cordarone X; Cordilox; Cyclospasmol; Cyklokapron; Cystrin; Cytotec; De-Nol; Derbac-M; Dermamist DHC Continus; Diamicron; Diamox SR; Dianette; Diazemuls; Diazepam Rec-Tubes; Diclomax Retard; Didronel PMO; Diflucan; Dimotane; Dimotane LA; Dioralyte; Dipentum; Diprosone; Distaclor; Distalgesic; Dithrocream; Ditropan; Diurexam; Dopram; Drogenil; Dulphalac; Dutonin; Efexor; Eldepryl; Elocon; Eminase; EMLA cream; Emulsiderm; Entocort Enema; Erymax; Erythroped; Eucardic; Evorel; Exirel; Fematrix; Ferrocontin Folic; Flexin; Flixonase; Flixotide; Flosint; Fluvirin; Forane; Fortral; Froben; Frumil; Fybozest; Gamanil; Gastron; Gopten; Haemaccel; Haycrom; Hexabrix; Hexabrix 320; Hismanal; Humatrope; Humulin; Hypovase; Hytrin; Ibugel; Imigran; Imodium; Influenza vaccine; Inhalers; Innovace; Insulin; Interferon beta-1a; Iocare; Iodosorb; Isoflurane; Isotrate; Ivelip; Kalspare; Kaltocarb; Kaltostat; Keflex; Klaricid; Lamictal; Lariam; Lasoride; Lederspan; Lejfibre biscuits; Lignocaine; Lipantil; Lipobay; Lipofundin MCT/LCT; Lipostat; Livostin Eye Drops and Nasal Spray; Macrodantin; Manerix; Manevac; Marvelon; Meptid; Mercilon; Metrogel; MFV-Ject Influenza vaccine; Minitran; Mintec; Mirena; Moduretic; Molipaxin; Morcap SR; Motilium; Mucodyne; Muphoran; Nasonex; Neurontin; Nicorette; Nifensar XL; Nitro-Dur; Noctamid; Normegon; Nutriflex; Nycopren; Omnipaque; Opitray; Oruvail; Oruvail 200; Oxivent; Panadeine Forte; Panadeine Tablets; Panadol Soluble; Penmix 30/70; Pepcid PM; Peptimax; Physiotens; Ponstan; Ponstan Forte; Praxilene; Praxilene Forte; Pred-Forte; Predfoam; Premique Priadel; Prograf; Propess; Prothiaden; Rifater; Rocephin; Salamol; Salazopyrin En-tabs; Salbuvent; Sandimmun; Securopen; Septrin; Septrin Forte; Skinoren; Solpadeine; Somatonorm; Sopronax; Stemetil Eff; Stesolid; Stugeron; Sucralfate; Suprax; Surgam; Surgam SA; Suscard; Suscard Buccal; Sustac; Syntaris; Tachyrol; Tarivid; Temazepam; Temgesic; Tenif; Tenoretic; Tetanus vaccine; Tilade; Tilade Mint Syncroner; Tildiem Retard; Topicycline; Toradol; Transvasin; Tranxene; Traxam; Traxam Foam; Triclosan; Triludan; Triludan Forte; Trinovum; Turbohaler; Unigam; Urispas; Vagifem; Variclene; Varidase; Vectavir; Velosef; Ventolin; Veracur Gel; Vibramycin; Voltarol;Viscoat; Xanax; Xatral; Zamadol; and Zyprex

Two cases:
Adalat Retard; Airomir; AmBisome; Asacol; Augmentin; Avaxim; Axid; Azactam; Becotide; Betagan; Bonefos; Cardene; Clexane; Combivent; Cuplex Gel; Cytotec; Desmospray; Diskhaler; Ditropan; Euhypnos; Flomax; Fucithalmic; Genotropin; Haymine; Ikorel; Influvac; Istin; Junifen; Lodine; Logynon; Lopid; Malinal; Miraxid; Mobic; Movelat; Naprosyn Low Excipient Tabs; Natrilix; Norcuron; Novantrone; Nubain; Orelox; Paramol; Phyllocontin Continus; Progynova TS; Provisc; Prozac; Pulmicort; Puregon; Regulan; Relifex; Saizen; Surmontil; Traxam Gel; Trinordiol; Volmax; Zinacef; Zithromax; and Zydol.

Three cases:
Adifax; Becodisks; Betoptic; Bezalip Mono; Bolvidon; Capoten; Capozide; Celectol; Clarityn; Coversyl; Curosurf; Curatoderm; De-Noltab; Engerix B; Feldene; Femodene; Kliofem; Lamisil; Maalox Suspension; Minocin; Minulet; MST Continus; Pecram; Securon SR; Seroxtat; Topamax; Vascace; Zinnat; and Zirtek.

Four cases:
Aerocrom; Ciproxin; Coversyl; Fareston; Lustral; Migraleve; Mobiflex; Neupogen; and Tildiem.

Five cases:
Alimix; Dovonex; Foradil; Losec; Pulmicort; Valtrex; and Zantac.

Six cases:
Actilyse; Faverin; Lederfen; and Motens.

Seven cases:
Adalat; Bricanyl Turbohaler; Famvir; Monocor; Serevent; and Tagamet.

Table A contd.

Nine cases: Rheumox and Zoton.
Ten cases: Zovirax.

Table B Analysis of complainants who have reported suspected breaches of the Code of Practice (1983 - 1997).

HEALTH PROFESSIONALS
One complaint: Assistant Pharmaceutical Adviser; Chairman of Local Research Ethics Committee; Chief Administrative Pharmaceutical Officer; Chief Hospital Pharmacist; Chief Pharmacist; Chief Pharmacist of NHS Trust Hospital; Chief Pharmacist on behalf of a Drug Review Committee; Clinical Director of a Hospital Pharmacy; Clinical Director of NHS Trust; Clinical Information Pharmacist; Clinical Pharmacy Manager; Community Health Council Chief Officer; Consultant Cardiologist and Physician; Consultant Dermatologist; Consultant in Ear, Nose and Throat; Consultant Gastroenterologist; Consultant Geriatrician and Drug Information Officer; Consultant Haematologist; Consultant Neurologist; Consultant Ophthalmologist; Consultant Orthopaedic Surgeon; Consultant Pharmaceutical Physician; Consultant Physician and Cardiologist; Consultant Physician and Endocrinologist; Consultant Physician/gastroenterologist; Consultant in the Psychiatry of Old Age; Consultant in Public Health/medical prescribing; Consultant Rheumatologist; Consultant Surgeon; Director of a Regional Drug Information Centre; Director of Medical Services at a Family Health Services Authority; Director of Primary Care Medicine; District Medical Officer; District Pharmaceutical Manager; Drug and Therapeutics Committee; Family Health Service Authority Clinical Director; Gastroenterologist; Gynaecologist; Head of a Department of Anaesthesia; Health Authority Quality Controller; Health Professional in a Hospital; Honorary Secretary of a Local Medical Committee; Hospital Chief Pharmacist; Hospital Consultant; Hospital Doctor; Hospital Information Pharmacist; Hospital Pharmacy Business Services Manager; Hospital Staff Pharmacist; Medical Adviser to a Family Health Services Authority; Medical Adviser to a Family Practitioner Committee; Medical Adviser to a Health Authority and Family Health Services Authority; Medical Group; Medical Director of a Family Health Services Authority; Medical Registrar; Member of a Medical Research Ethics Committee; Pharmaceutical Adviser to Health Body; Pharmaceutical Services Director; Pharmaceutical Services Negotiating Committee; Pharmacy Prescribing Facilitator; Pharmacy Services Manager; Physician; Physician Superintendent/Clinical Director of an NHS Trust; Practice Nurse Facilitator; Prescribing Adviser and Clinical Pharmacy Adviser at a Hospital; Primary Care Pharmacy Consultant; Principal Pharmacist with a Regional Health Authority; Professor of Clinical Microbiology; Professor of Clinical Pharmacology; Professor of Pharmacology; Reader in Therapeutics; Regional Director of Public Health; Regional Health Authority; Regional Health Authority Pharmaceutical Officer; Regional Health Authority's Commodity Advisory Group; Regional Principal Pharmacist; Regional Technical and Procurement Pharmacist; Secretary of a Local Research Ethics Committee; Senior Executive in a Regional Health Authority; Senior Pharmacist from a Drug Information Centre; University Doctor; University Hospital Professor of Surgery; and University Lecturer in Dermatology.

Table B contd.

Two complaints: Assistant Pharmaceutical Adviser with a Health Authority; Chairman of a Hospital Drug and Therapeutics Committee; Chief Pharmacy Services Manager; Child and Adolescent Consultant Psychiatrist; Clinician; Community Pharmacist; Consultant; Consultant Geriatrician; Consultant Microbiologist; Consultant in Pharmaceutical Medicine; Continence Adviser; Drug Information Pharmacist; Ethics Committee Chairman; General Practitioner Chairman of Medical Audit Advisory Group; Group of General Practitioners; Independent Medical Adviser; Information Pharmacist; Lecturer in Medicine; Medical Director of a Hospice; Medical Professor; NHS Manager; Nurse; Pharmaceutical Officer to a Family Health Service Authority; Pharmacist with NHS body; Regional Technical Pharmacist; Secretary of a Medical Committee; and University Lecturer.
Three complaints: Consultant Anaesthetist; Consultant Microbiologist; Consultant Paediatrician; Medical Adviser to a Family Health Services Authority; Medical Practitioner; Medical Prescribing Adviser; Pharmacist with a Regional Health Authority; and Senior Registrar.
Four complaints: Clinical Pharmacologist; Director of Pharmacy Services; District Pharmaceutical Officer; and Pharmaceutical Adviser.
Five complaints: Hospital Consultant; and Pharmaceutical Adviser with a Family Health Services Authority.
Six complaints: Drug Information Pharmacist; Hospital Doctor; and Principal Pharmacist.
Seven complaints: Consultant Paediatrician; Consultant Psychiatrist; and Staff Pharmacist.
Eight complaints: Pharmacist.
Nine complaints: Drug Information Pharmacist.
Twelve complaints: Community Pharmacist.
Fifteen complaints: Hospital Doctor.
Sixteen complaints: Member of the Medical Profession.
Eighteen complaints: Consultant Physician.

Table B contd.

Twenty complaints Hospital Pharmacist.
Twenty Three complaints: Doctor.
Two Hundred and Seventy Eight complaints: General Practitioner.
COMPANIES[1]
One complaint: 3M Health Care Limited; Abbott Laboratories Limited; A.H. Robins Company Limited; Alpha Therapeutic UK Limited (n/m); Antigen Pharmaceuticals (UK) Limited (n/m); APS/Berk; Ashbourne Pharmaceuticals Limited (n/m); Boehringer Ingelheim Limited; CCL plc; Ciba-Geigy Pharmaceuticals; Cyanamid of Great Britain Limited; Dumex (n/m); Du Pont Pharmaceuticals Limited; Ethical Pharmaceuticals; E.R. Squibb & Sons Limited; Evans Medical Limited; Fisons Pharmaceuticals; Fisons plc; ICI Pharmaceuticals Limited; Janssen Pharmaceutical Limited; Kabi Vitrum Limited (n/m); Lilly; Lipha Pharmaceuticals Limited; Lorex Synthelabo; Merck & Lipha; Monmouth Pharmaceuticals Limited (n/m); Norgine Limited (n/m); Norton Healthcare; Nycomed (UK) Limited (n/m); Panpharma Limited (n/m); Pasteur Merieux MSD Ltd; Perstorp Pharma Limited (n/m); Proctor & Gamble Pharmaceuticals UK Limited; Reckitt & Colman; Sandoz Pharmaceuticals (UK) Ltd; Sanofi Winthrop Limited; Schwarz Pharma Limited; Syntex Pharmaceuticals Limited; Warner Lambert (UK) Limited and; Zyma (UK) Limited.
Two complaints: Baker Norton; B. Braun Medical Limited (n/m); Biogen; Boehringer Mannheim UK (Pharmaceuticals) Limited; Duphar Laboratories Limited; Lederle Laboratories; Lorex Pharmaceuticals Limited; Lundbeck; Marion Merrell Dow Limited; Merrell Dow Pharmaceuticals Limited; Novo Nordisk Pharmaceuticals Limited (n/m); Rhône-Poulenc Rorer; Sanofi UK Limited; Schwarz Pharma Limited; Scotia Pharmaceutical Limited (n/m); Servier Laboratories Limited (n/m); Smith Kline & French Laboratories Limited; Solvay Healthcare Limited; Seton Healthcare (n/m); Steifel Laboratories (n/m); Wyeth; and Yamouchi Pharma Limited.
Three complaints: Alcon Laboratories Limited (n/m); Allergan (UK) Limited; Ciba Pharmaceuticals; E. Merck; Farmitalia Carlo Erba Limited; Janssen-Cilag; Merck Sharp & Dohme Limited
Four complaints: Dermal Laboratories Limited (n/m); Searle; Serono Laboratories (UK) Limited (n/m); Upjohn Limited; and Zeneca Pharma.

[1] n/m means non-member company.

Table B contd.

Five complaints: Leo Laboratories Limited; Napp Laboratories Limited (n/m); Organon Laboratories Limited; Parke Davis & Company Limited; Schering Health Care Limited; and Smith & Nephew Pharmaceuticals Limited.
Six complaints: Glaxo Wellcome; and Wellcome Foundation Limited.
Seven complaints: Kabi Pharmacia Limited (n/m); Pfizer Limited; and Pharmacia Limited (n/m).
Eight complaints: Allen & Hanburys Limited; Astra Pharmaceuticals Limited (n/m); and Glaxo Laboratories Limited.
Eleven complaints: SmithKline Beecham Pharmaceuticals UK Limited.
Fourteen complaints: Non-Member Company. (not specified in reports)
Ninety four complaints: Member Company. (not specified in reports).
PRESCRIPTION MEDICINES CODE OF PRACTICE AUTHORITY
One complaint: Article in the Pharmaceutical Press; Letter published in the Pharmaceutical Press; The Daily Mirror; The News of the World; Newspaper article; The Observer; The Sun; The Sunday Sport; and The Yorkshire Post.
Two complaints: The Guardian.
Four complaints: Article published in the National Press; Letter published in a Medical Journal; Letter published in The Pharmaceutical Journal; and The Sunday Times.
Five complaints: Letter published in The British Medical Journal.
Six complaints: Breach of undertaking.

Table B contd.

Eight complaints: Advertisement scrutiny; and Drug and Therapeutics Bulletin.
Twelve complaints: "First Tuesday".
Fourteen complaints: Letter published in the Lancet
Eighteen complaints: Paragraph 16 Procedure.[2]
MISCELLANEOUS
One complaint: British Medical Association; Consumer Body; Freelance Journalist; Information Council; Medical Society; Member of Parliament; Member of the Public; Patient Group; The National Medical Advisers Support Centre; National Pharmaceutical Association; and the World Health Organisation.
Two complaints: Pharmaceutical Society of Great Britain; Professional Medical Body and Royal College of Physicians.
Three complaints: International Federation of Pharmaceutical Manufacturers' Association.
Five complaints: Department of Health and Social Security.
Six complaints: Medicines Control Agency.
Fifteen complaints: Anonymous.

[2]This procedure is utilised where the Code of Practice Panel or the Code of Practice Appeal Board identify a possible breach of the Code of Practice which has not been addressed by the complainant.

Table C Companies in breach of the Code of Practice (1983 - 1996)

One case:

Antigen Pharmaceuticals (UK) Limited (n/m); Aurum; Baker Norton; B. Braun Medical Limited (n/m); Beecham Group plc; Beecham Research Laboratories; Beerse Research (a division of Janssen Pharmaceutical Limited); Bristol-Myers Pharmaceuticals; Charwell Pharmaceuticals; Ciba-Geigy Pharmaceuticals; CibaVision; Clintec Nutrition Limited (n/m); CP Pharmaceuticals; Cyanamid UK; Delandale Laboratories Limited; Dista Products Limited; Dorsey Laboratories; Ferring Pharmaceuticals Limited (n/m); Fujisawa; Galen Limited (n/m); Geigy Pharmaceuticals; Gist-Brocades Pharmaceuticals; Glaxo Wellcome; Gold Cross Pharmaceuticals (a division of G.D. Searle & Company Limited); Guerbert Laboratories Limited (n/m); Hocchst Marion Roussel; Houghs; Innovex; Lorex Synthelabo; Merck & Lipha Pharmaceuticals; Merieux UK Limited; Nordisk - UK Limited (n/m); Norton Healthcare; Novartis; Orion Pharma; Ortho Division of Cilag Limited; Pharmacia Leiras Limited (n/m); Proctor & Gamble Pharmaceuticals UK Limited; Riker Laboratories; Sanofi UK Limited; Sanofi Winthrop; Schering Pharmaceuticals; Schwarz Pharma Limited; Seton Healthcare (n/m); Smith Laboratories Limited; Smith & Nephew Medical; Solvay Health Care Limited; Sterling Research Laboratories; Sterling Winthrop Group Limited; Storz Ophthalmics Limited (a division of Cyanamid of GB Limited); Thomas Morson Pharmaceuticals (a division of Merck, Sharp & Dohme Limited); Typharm Limited (n/m); UCB Pharma Limited (n/m); Warner Lambert (UK) Limited; Wellcome plc; Wyeth Lederle; and Zeneca Pharma.

Two cases:

Amgen Limited; Armour Pharmaceutical Company Limited; Beecham Pharmaceuticals; Berk Pharmaceuticals Limited; Boehringer Mannheim Limited; Boots Pharmaceuticals Limited; BritCair Limited (n/m); Dumex Limited (n/m); Evans Medical Limited; Fisons plc; Kabi Pharmacia Limited (n/m); KabiVitrum Limited (n/m); Knoll Limited; Mallinckrodt Medical (UK) Limited (n/m); MCP Pharmaceuticals Limited; Merrell Dow Pharmaceuticals; Norgine Limited (n/m); Nycomed (UK) Limited (n/m); Organon Teknika Limited; Pasteur Merieux MSD; Princeton Pharmaceuticals (part of E.R. Squibb & Sons Limited); Reckitt & Colman Pharmaceuticals; Schering Chemicals Limited; Stafford Miller Limited (n/m); Stuart Pharmaceuticals Limited; Tillotts Laboratories (n/m); Vestar Limited (n/m); and Winthrop Laboratories.

Three cases:

Allergan Limited; Ashbourne Pharmaceuticals Limited (n/m); Bioglan Laboratories Limited (n/m); Britannia Pharmaceuticals Limited; Du Pont Pharmaceuticals Limited; Eli Lilly & Company Limited; G.D. Searle and Company Limited; Glaxo Pharmaceuticals Limited; Kirby-Warrick Pharmaceuticals; Lipha Pharmaceuticals; Lundbeck Limited (n/m); May & Baker Limited; May & Baker Pharmaceuticals; Merck, Sharp & Dohme Limited; Norwich Eaton Limited; Panpharma Limited (n/m); Pharmacia Limited (n/m); Sandoz Pharmaceuticals (n/m); Upjohn Limited; Yamanouchi Pharma Limited.and Zyma (UK) Limited.

Four cases:

3M Health Care; Asta Medica Limited (n/m); Ayerst Laboratories Limited; Bayer plc; Boots Company plc; Brocades (GB) Limited; Farmitalia Carlo Erba Limited; Hocchst UK Limited; International Laboratories Limited (n/m); Janssen Pharmaceutical Limited; Novo Nordisk Pharmaceuticals Limited (n/m); Rorer Pharmaceuticals; Roussel Laboratories Limited; and Searle.

Five cases:

Ciba Pharmaceuticals; E. Merck Limited; Janssen-Cilag; Knoll Pharma Limited; Lorex Pharmaceuticals Limited (n/m and division of Searle); and Schering-Plough Limited.

Table C contd.

Six cases: Alcon Laboratories Limited(n/m); Bristol-Myers Squibb Pharmaceuticals Limited; Dermal Laboratories Limited (n/m); Duncan Flockhart & Company Limited; Fisons Pharmaceuticals; Lilly Industries Limited
Seven cases: Abbott Laboratories Limited; Cilag Limited; Serono Laboratories (UK) Limited (n/m); E.R. Squibb & Sons Limited; and Smith & Nephew Pharmaceuticals Limited.
Eight cases: Organon Laboratories Limited; Pharmax Limited (n/m); Syntex Pharmaceuticals Limited; and Wyeth Laboratories Limited.
Nine cases: Duphar Laboratories Limited; Parke & Davis Research Laboratories; and Schering Health Care Limited.
Ten cases: Leo Laboratories Limited (n/m and later member).
Twelve cases: Bayer UK Limited; and Rhône-Poulenc Rorer Limited.
Thirteen cases: A.H. Robins and Company Limited; Napp Laboratories Limited (n/m); Roche Products Limited; and Smith Kline & French Laboratories Limited.
Fourteen cases: Glaxo Laboratories Limited
Fifteen cases: Servier Laboratories Limited (N/M).
Sixteen cases: The Wellcome Foundation Limited; and Pfizer Limited.
Seventeen cases: Lederle Laboratories; and SmithKline Beecham Pharmaceuticals.
Twenty two cases: Allen & Hanburys Limited.

Table C contd.

Twenty three cases: Astra Pharmaceuticals Limited (n/m and later member).
Twenty four cases: Boehringer Ingelheim Limited.
Thirty cases: Lederle Laboratories.

Table D Analysis of Breaches of the ABPI's Code of Practice for the Pharmaceutical Industry (1983 - 1996).

	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
Discredit to and reduction of confidence in the pharmaceutical industry [CLAUSE 2; *formerly clause 2*]	1	5	6	2	3	0	4	6	7	2	5	5	1	3
Promotion prior to the grant of a marketing authorisation [CLAUSE 3; *formerly clause 3*]	0	1	0	0	0	1	5	2	1	2	1	6	4	4
Clear and legible prescribing information [CLAUSE 4.1; *formerly clauses 7.1 and 7.3*]	4	13	8	2	6	3	10	2	4	7	7	10	5	9
Audio material [CLAUSE 4.4; *formerly clause 13.2*]	0	0	0	7	0	0	0	0	0	0	0	0	0	0
Two page journal advertisements [CLAUSE 4.5; *formerly clause 7.13*]	0	2	0	0	0	0	0	1	0	0	1	0	0	0
Multi-page advertisements [CLAUSE 4.6; *formerly clause 7.14*]	0	0	0	0	0	0	0	0	1	0	0	2	0	1
Abbreviated advertisements [CLAUSE 5; *formerly clause 7.4*]	1	0	0	0	0	0	0	1	1	0	0	2	0	0
Advertisements in journals [CLAUSE 6.1; *formerly clause 7.10*]	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Limitation on numbers of pages of advertising [CLAUSE 6.4]	-	-	-	-	-	-	-	-	-	-	-	-	-	1

Table D contd

	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
Misleading information, claims and comparisons [CLAUSE 7.2; *formerly clauses 4.2, 4.3 and 5.1*]	10	9	10	16	21	18	22	20	18	25	27	66	38	49
Substantiation of information, claims and comparison [CLAUSES 7.3 AND 7.4; *formerly clauses 4.4 and 5.5*]	7	6	8	8	10	9	15	13	8	9	5	5	2	11
References to published studies [CLAUSE 7.5]	-	-	-	-	-	-	-	-	-	-	2	0	0	0
Misleading use of artwork, illustrations, graphs and tables [CLAUSE 7.6; *formerly clause 10.3*]	0	0	4	0	1	1	3	4	2	3	1	4	4	1
Side effects [CLAUSE 7.7; *formerly Clause 5.3*]	1	3	2	1	3	3	0	2	0	0	0	2	1	6
Exaggerated or all-embracing claims [CLAUSE 7.8; *formerly clause 5.2*]	8	10	16	7	8	14	7	5	3	12	7	11	0	5
Use of brand names [CLAUSE 7.10; *formerly Clause 5.6*]	0	2	0	0	1	0	1	0	0	2	0	1	0	1
Disparaging references [CLAUSES 8.1 AND 8.2; *formerly clause 6.1*]	0	1	0	0	0	5	0	4	1	3	0	5	5	3
Suitability and Taste [CLAUSE 9.1; *formerly clause 7.6*]	1	1	0	0	0	2	0	4	2	2	2	10	2	1

Table D contd.

	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
Names or photographs of health professionals [CLAUSE 9.2; *formerly clause 7.7*]	0	1	0	0	0	0	0	0	0	1	0	0	0	0
References to Licensing Authority, Medicines Commision, CSM etc. [CLAUSE 9.4; *formerly clause 8*]	1	0	0	0	0	0	2	0	0	0	0	0	0	0
Reproduction of official documents [CLAUSE 9.5; *formerly Clause 9.2*]	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Extremes of format [CLAUSE 9.6; *formerly clause 7.10*]	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Sponsorship [CLAUSE 9.9]	-	-	-	-	-	-	-	-	-	-	-	-	-	2
Disguised promotional material [CLAUSES 10.1; *formerly clause 7.5*]	1	0	1	1	1	1	1	0	2	2	2	6	1	2
Marketing research [CLAUSE 10.2; *formerly clauses 21.1, 21.2 and 21.4*]	0	0	0	0	0	2	5	1	0	0	0	0	0	1
Reprints [CLAUSE 11.1; *formerly clause 11.1*]	0	1	0	1	0	0	0	0	0	0	0	0	0	0
Use of quotations from medical literature [CLAUSE 11.2; *formerly Clause 11.2*]	0	0	1	1	0	1	0	0	1	0	1	2	0	0

Table D contd

	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
Quotations from public broadcasts [CLAUSE 11.3; *formerly clause 11.3*]	0	0	0	0	0	0	0	0	0	2	0	0	0	0
Ascribing claims or views [Clause 11.4]	-	-	-	-	-	-	-	-	-	-	-	-	-	1
Distribution of promotional material [CLAUSE 12.1; *formerly clause 12.1 and 12.2*]	0	0	1	0	0	0	0	1	0	0	0	1	0	0
Certification of printed promotional material [CLAUSE 14.1; *formerly clause 15.1*]	0	0	1	0	1	0	0	0	0	2	0	0	0	0
Training of medical representatives [CLAUSE 15.1; *formerly clause 17.1*]	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Ethical conduct of medical representatives [CLAUSE 15.2; *formerly clauses 17.2, 17.3 and 17.4*]	2	1	0	1	0	5	3	3	1	2	7	9	5	3
Inducement or subterfuge to gain interview [CLAUSE 15.3; *formerly clause 17.6*]	1	0	0	0	1	1	2	2	2	2	0	1	1	1
Frequency, timing and duration of calls by medical representatives [CLAUSE 15.4; *formerly clause 17.7*]	0	0	0	0	0	1	0	0	0	0	0	1	0	0

Table D contd

	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
SPC to be provided by medical representatives [CLAUSE 15.9; *formerly clause 17.11*]	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Detailedbriefing material to be given by companies to medical representatives [CLAUSE 15.9; *formerly clause 17.12*]	0	0	0	0	0	0	0	0	0	0	2	0	0	0
Samples provided only in response to a signed request [CLAUSE 17.3; *formerly clause 18.1*]	0	0	1	0	1	0	1	0	1	0	2	0	0	1
Sample to be marked as such and accompanied by the SPC [Clause 17.5]	-	-	-	-	-	-	-	-	-	-	-	-	-	1
Samples must be handed to health professionals [CLAUSE 17.7; *formerly clause 18.4*]	0	0	1	0	0	0	0	0	0	0	0	0	0	0
System of control over samples [CLAUSE 17.9]	-	-	-	-	-	-	-	-	-	-	0	0	1	0
Samples sent by post [CLAUSE 17.10; *formerly clause 18.3*]	0	0	0	0	0	2	0	0	1	0	0	0	0	0
Financial inducements or gifts [CLAUSES 18.1 AND 18.2; *formerly clause 19.1*]	2	3	3	1	2	1	1	1	2	2	4	3	2	3

Table D contd

	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
Hospitality [CLAUSE 19.1; *formerly clause 20*]	3	3	0	0	1	0	1	7	1	0	5	6	0	1
Prescription only medicines must not be advertised to the public [CLAUSE 20.1; *formerly clause 22.1*]	0	0	0	0	0	0	0	0	0	1	0	0	2	0
Information to members of the public [CLAUSE 20.2; *formerly clause 22.2*]	0	0	0	2	1	1	0	0	1	3	0	2	3	2
Requests for information [CLAUSE 20.3; *formerly clause 22.3*]	0	0	0	0	1	1	1	0	1	0	0	0	0	0
Introduction of a new medicine [CLAUSE 20.4; *formerly clause 22.4*]	0	1	0	1	2	2	1	1	0	0	0	0	0	0
Compliance with Undertakings [Clause 21]	-	-	-	-	-	-	-	-	-	-	-	-	-	1

Appendix XXVIII

Selected examples of Cases involving a Breach of the Code of Practice of the Pharmaceutical Industry (1996 - 1997)

Anonymous v Pfizer [Case Auth/478/11/96]

Breach of Clause 19

An anonymous complaint was received about a meeting held by Pfizer with a doctor from a hospital in relation to problems with a clinical trial. The meeting consisted of a visit to the opera followed by dinner. There were six attendees, the doctor and his wife, the company medical adviser, a clinical research project manager and the medical representative for the hospital and his wife.

The Panel ruled that the meeting came within the scope of the Code. The clause relating to meetings, clause 19, made it clear that the Code applied to all meetings with members of health professions regardless of whether any meeting itself was promotional or not. The Panel ruled that the hospitality was unacceptable given the events and the inclusion of the doctor's wife. This was accepted by Pfizer. The Panel ruled a breach of Clause 2 as the events brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel also decided to report Pfizer to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure. Pfizer appealed the ruling of the breach of clause 2.

The Appeal Board noted that the meeting was a discussion with a clinical trialist. It was a non-promotional meeting. Given the nature of the meeting and the facts of this particular case, the Appeal Board considered that it did not warrant a ruling of a breach of Clause 2 of the Code. The appeal was successful. Given the ruling of no breach of clause 2, the Appeal Board decided that there was no need to take ant further action regarding the report from the Panel.

Consultant Dermatologist v Wyeth [Case Auth/486/1/97]

Breach of Clauses 2, 9.1 and 10.1

A consultant dermatologist complained about a letter referring to Wyeth's product Minocin (minocycline) which had been circulated to doctors by Wyeth.

The complainant had been asked by Wyeth to write to local doctors because many patients who were well established on minocycline for their acne had been taken off it because of worry about lupus erythematosus like symptoms. The letter had, however, been circulated more widely than the consultant's immediate catchment area and had been retyped with a different date and title. The title had been changed from "Should minocycline ever be prescribed for the treatment of acne" to "Minocycline for the treatment of acne". The Trust logo of the hospital at which the consultant was based had been reproduced on the letter and the envelope.

The Panel considered the change in the title to be a serious matter as it completely changed its meaning. It was up to anyone reproducing a letter in this way to have a high standard of checking. The copying of the Trust logo was also a serious matter, particularly on the envelope as this was a tactic likely to ensure prompt attention by recipients. The Panel considered that high standards had not been maintained and that the use of the logo on the envelope and the failure to reveal Wyeth's role amounted to disguised promotion. These rulings were accepted by Wyeth.

The Panel also considered that the circumstances had brought discredit upon the industry and so ruled. This ruling was appealed by Wyeth but confirmed on appeal by the Code of Practice Appeal Board.

Consultant Psychiatrist v Wyeth Lederle [Case Auth/452/8/96]

Breaches of Clauses 6.4, 9.9 and 10.1

A consultant psychiatrist alleged that a seemingly independent edition of the journal "Psychiatry in Practice" was in fact sponsored by Wyeth for the promotion of Efexor.

The Panel noted that Wyeth's declaration of sponsorship was not obvious to readers of the journal and a breach of the Code was ruled. The Panel also noted that, in addition to three pages of advertising for Efexor, the journal contained a sponsored review on the use of the product in the elderly. The journal thus bore advertising for Efexor on more than 3 pages in breach of the Code.

The Panel considered that the editorial content of the journal was acceptable and ruled no breach of the Code. On appeal from the complainant the Appeal Board ruled a breach of the Code, considering that one article was a promotional piece for Efexor disguised as independent copy.

Director v Ciba [Case Auth/521/3/97]

Breach of Clauses 2 and 21

Glaxo Wellcome alleged that Ciba Pharmaceuticals was continuing to use a leavepiece which had previously been ruled to be in breach of the Code. The matter was taken up by the Director of the Authority as a complaint under the Code.

The Panel noted that although Ciba had made considerable efforts to withdraw the item in question it appeared that not all the copies of the leavepiece had been returned to head office. It had been let down by its representatives for whom it must take responsibility. Ciba had failed to comply with its undertaking and a breach of the Code was ruled. The company's failure to comply with the undertaking brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel therefore ruled a breach of Clause 2 of the Code.

Director/Scrutiny v Norton Healthcare [Case Auth/421/4/96]

Breach of Clause 18.1

An advertisement for certain prescription only medicines issued in association with Norton Healthcare was taken up during the routine scrutiny of journal advertisements. The advertisement offered Marks & Spencer's vouchers and/or a mountain bike when purchasing certain prescription only medicines. As the matter could not be settled it was referred to the Panel as a case.

The Panel ruled that the offer of Marks & Spencer's vouchers and mountain bikes was an inducement to health professionals to purchase prescription medicines. A breach of the Code was ruled. This ruling was upheld by the Appeal Board on appeal by Norton Healthcare.

E. Merck v Leo [Case Auth/453/8/96]

Breach of Clause 8.1

E. Merck complained about a conference poster used by Leo, which drew attention to a competition in which delegates were invited to show, by marking a bar chart , the relative efficacy of tacalcitol compared to that given for Dovonex. Merck alleged that the use of a question mark instead of a bar for tacalcitol was disparaging and suggested a level of efficacy for the product which could not be substantiated.

The Panel did not accept that the question mark implied a specific efficacy for tacalcitol but did consider that its use was disparaging because it implied that the efficacy of tacalcitol was in doubt. A breach of clause 8.1 was ruled.

Hospital Pharmacist v Lilly [Case Auth/497/2/97]

Breach of Clause 15.2

A hospital pharmacist complained about the conduct of a representative from Eli Lilly. It had been reported to the complainant that the representative had said at a group meeting that a competitor product had been withdrawn on the grounds of patient safety. The complainant had confirmed with the competitor company that this information was incorrect.

The Panel noted that it was untrue to say that the competitor product had been withdrawn from the market on the grounds of patient safety. Although the representative had tried the next day to correct the false impression he had given about the competitor product, the Panel ruled that he had not maintained a high standard of ethical conduct and had failed to comply with all the relevant clauses of the Code.

Seton v Houghs [Case Auth/441/6/96]

Breach of Clauses 3.1, 3.2 and 4.1

Seton Healthcare complained that a practical information document on Triclosan and MRSA, issued by Houghs Healthcare, lacked prescribing information, promoted off licence indications and formulations and lacked supporting references.

The Panel noted that the document was part of a standard information pack supplied in response to all general enquiries. The pack contained promotional items and the information given in the document was not tailored to the needs of the specific enquirers. The document was viewed as promotional and the Panel ruled breaches of the Code with respect to the lack of prescribing information and the mention of off licence indications and formulations. No breach of the Code was ruled regarding substantiation of certain claims.

Yamanouchi v Bioglan (N/M) [Case Auth/461/9/96]

Breaches of clauses 7.2 and 10.1

Yamanouchi complained about a journal advertisement and a mailing on Benzamycin issued by Bioglan. There were six allegations.

The Panel ruled that the advertisement resembled editorial matter in breach of the Code. The Panel also ruled that a diagram was misleading in that it had not been made clear that the diagram in the advertisement had been modified from that in the quoted reference. No breach of the Code was ruled in relation to a reference to 72 patients being involved in a study whereas only 67 patients completed the actual study. The Panel ruled no breach of the Code with regard to an allegation that data from a study implied that 67% of patients found Benzamycin acceptable. No breach of the Code was ruled in relation to the mention of a health professional's name in the advertisement. Finally, no breach of the Code was ruled in relation to the omission of a bar from a bar chart, given that in these particular circumstances the layout was such that readers would not be misled.

Yamanouchi v Lorex Synthélabo [Case Auth/492/1/97]

Breaches of Clauses 7.2, 7.3, 7.8 and 18.1

Yamanouchi complained about the promotion of Xatral by Lorex Synthélabo.

The Panel ruled no breach of the Code with regard to an allegation that claims relating to use of the terms "uroselective", "clinical uroselectivity" and "uroselective and effective". were misleading, all embracing and had not been substantiated to Yamanouchi on request. The Panel ruled a breach as it considered that eyeshades provided to doctors as a promotional aid were not relevant to the practice of medicine. No breach of the Code was ruled with regard to a wrapper advertisement alleged to fail to state where the prescribing information could be found. A claim "To avoid close encounters of the BPH kind" was ruled in breach as it implied the product would work in 100% of patients and this was not so. A statement that Xatral did not require initial dose titration was not considered to be promotion outside the licence and no breach was ruled

Zeneca Pharma, Hospital Doctor, Hospital Doctor and Director/Media v Orion Pharma (non-member company) [Case Auth/446/7/96, 449/7/96, 467/10/96 & 470/10/96]

Breaches of clauses 3.2, 4.1, 7.2 and 7.7

Three complaints (from Zeneca and two hospital doctors) were received about the promotion of Fareston by Orion Pharma. A letter published in the British Medical Journal criticising the promotion of Fareston was taken up as a further complaint in accordance with established procedure.

The Panel ruled that the material at issue, three journal advertisements and a brochure, was misleading and unbalanced in breach of the Code. There was insufficient evidence to support the impression given that tamoxifen was linked clinically with cancer and Fareston was not. Too much was made of the limited animal data given that its relevance to the clinical situation was not certain. These rulings applied in all four cases and were upheld by the Appeal Board on appeal by Orion Pharma.

Zeneca alleged that one advertisement was a teaser advertisement. The Panel decided that the advertisement gave too much information for it to be a teaser. Readers would know that the product was for breast cancer. A breach of the Code was ruled as no prescribing information had been provided.

The Panel accepted an allegation from Zeneca that the impression of an advertisement was that the indication for Fareston was unrestricted and similar to that of tamoxifen. This was not so. Fareston was licensed for first line hormone treatment of hormone dependent metatastic breast cancer in post menopausal patients and tamoxifen was licensed for the treatment of breast cancer. The Panel ruled that the advertisement promoted Fareston outside its product licence and was misleading.

Appendix XXIX

Medicinal Products examined by the CSM (1970 - 1997)

ACE-Inhibitors	Current Problems No.27 [1989]; Current Problems No.33 [1992]; Current Problems No.35 [1992]
Actifed Syrup	Current Problems No.14 [1985]
Alclofenac	Annual Report [1973]
Alendronate sodium [Fosamax]	Current Problems in Pharmacovigilance [July 1996]
Alphadalone and Alphaxalone [Althesin]	Current Problems No.2 [1976]; Current Problems No.3 [1978]; Current Problems No.4 [1979]
Alternative medicines	Current Problems No.16 [1986]
Aminocaproic Acid [Epsikapron]	Current Problems No.8 [1982]
Amiodarone [Cordarone X]	Current Problems No.8 [1982]; Current Problems No.13 [1984]; Current Problems No.16 [1986]; Current Problems in Pharmacovigilance [March 1996]
Amphotericin	Current Problems in Pharmacovigilance [July 1996]
Ampicillin	Current Problems No.15 [1985]
Anaesthetic agents	Annual Report [1978]; Current Problems in Pharmacovigilance [May 1997]
Antibiotics	Current Problems in Pharmacovigilance [May 1994]
Anticonvulsants	Dear Doctor Letter [May 1973]
Anti-HIV drugs	Current Problems in Pharmacovigilance [May 1997]
Aspirin	Annual Report [1973]; Annual Report [1985]; Dear Doctor Letter [10 June 1986]; Annual Report [1987]; Current Problems in Pharmacovigilance [February 1993]
Astemizole [Hismanal]	Current Problems No.19 [1987]; Current Problems No.35 [1992]
Atracurium Besylate	Current Problems No.14 [1985]
Azapropazone [Rheumox]	Current Problems in Pharmacovigilance [May 1994]
Baclofen [Lioresal]	Current Problems in Pharmacovigilance [February 1997]
Bal Jivan Chamcho	Annual Report [1976]
Barbiturates	Current Problems in Pharmacovigilance [July 1996]
BCG Vaccine	Current Problems No.16 [1986]
Benorylate [Benoral]	Current Problems No.16 [1986]
Benoxaprofen [Opren]	Dear Doctor Letter [1982]

Benzodiazepines	Current Problems No.21 [1988]
Beta-blockers	Current Problems No.1 [1975]; Dear Doctor Letter [1976]; Annual Report [1977]; Annual Report [1979]; Current Problems No.20 [1987]; Current Problems No.28 [1990]; Current Problems in Pharmacovigilance [March 1996]
β_2-Agonists	Current Problems No.28 [1990]; Current Problems No.31 [1990]; Current Problems No.33 [1992]
Blood Products	Annual Report [1985]; Annual Report [1986]
Botulinum Type A Toxin [Dysport]	Current Problems in Pharmacovigilance [November 1993]
Bupivacaine [Marcain Plain]	Current Problems No.12 [1983]
Calcipotriol [Dovonex Ointment]	Current Problems in Pharmacovigilance [February 1994]
Calcium Channel Blockers	Current Problems in Pharmacovigilance [February 1997]
Carbamazepine	Current Problems in Pharmacovigilance [June 1993]
Carbimazole	Current Problems No.32 [1992]
Cephalosporins	Current Problems No.3 [1978]; Current Problems No.32 [1992]
Chloramphenicol	Annual Report [1973]
Chlopromazine	Current Problems No.18 [1986]
Chloraseptic Throat Spray	Current Problems No.28 [1990]; Annual Report [1992]
Chlorhexidine	Annual Report [1972]
Chlormethiazole [Heminevrin]	Current Problems No.20 [1987]
Chloroform	Annual Report [1977]; Annual Report [1978]
Cimetidine [Tagamet]	Current Problems No.6 [1981]; Current Problems No.7 [1981]
Ciprofloxacin [Ciproxin]	Current Problems No.22 [1988]; Current Problems No.32 [1992]
Cisapride [Prepulsid; Alimix]	Current Problems in Pharmacovigilance [February 1995]; Current Problems in Pharmacovigilance [March 1996]
Clarithromycin [Klaricid]	Current Problems No.35 [1992]
Clindamycin [Dalacin C]	Current Problems No.2 [1976]; Adverse Reactions Series No.17 [1979]
Clioquinol	Annual Report [1972]; Dear Doctor Letter [May 1973]

Clofibrate [Atromid S, Liprinal]	Current Problems No.3 [1978]; Current Problems No.4 [1979]; Adverse Reaction Series Leaflet No.18 [1980]
Clomiphene [Clomid and Serophene]	Current Problems in Pharmacovigilance [July 1995]
Clomipramine	Current Problems No.18 [1986]
Clozapine [Clozaril]	Current Problems No.30 [1990]; Current Problems No.31 [1991]; Current Problems in Pharmacovigilance [November 1993]
Co-Amoxiclav [Augmentin]	Current Problems in Pharmacovigilance [February 1993]; Current Problems in Pharmacovigilance [May 1997]
Co-trimoxazole [Septrin, Bactrim and various generic preparations]	Annual Report [1977]; Current Problems No.15 [1985]; Current Problems in Pharmacovigilance [July 1995]
Corticosteroids	Current Problems in Pharmacovigilance [February 1994]; Current Problems in Pharmacovigilance [October 1996]; Current Problems in Pharmacovigilance [February 1997]
Cyancobalamin [Cytamen, Hepacon B_{12}]	Current Problems No.6 [1981]
Cyclosporin	Current Problems in Pharmacovigilance [February 1997]
Cyproterone acetate [Cyprostat, Androcur]	Annual Report [1994]; Current Problems in Pharmacovigilance [February 1995]
Dalkon Shield	Current Problems No.15 [1985]
Debendox	Current Problems No.6 [1981]
Depo Provera	Annual Report [1981]
Desensitising Vaccines [allergen extracts]	Dear Doctor Letter [8 October 1986]; Current Problems in Pharmacovigilance [May 1994]
Dexfenfluramine [Adifax]	Current Problems No.34 [1992]; Current Problems in Pharmacovigilance [June 1993]; Current Problems in Pharmacovigilance [February 1997]
Dextropropoxyphene	Current Problems No.4 [1979]; Current Problems No.14 [1985]; Current Problems No.17 [1986]
Diazepam	Current Problems No.3 [1978]
Diethylpropion	Annual Report [1988]
Diflunisal [Dolobid]	Current Problems No.4 [1979]
Digoxin [Lanoxin]	Dear Doctor Letter [2 August 1972]; Annual Report [1974]; Annual Report [1975]
Dothiepin	Current Problems No.18 [1986]

Doxycycline	Current Problems No.27 [1989]
Emepronium Bromide	Current problems No.3 [1976]
Enalapril [Innovace]	Current Problems No.17 [1986]
Erythromycin	Current Problems No.7 [1981]; Annual Report [1987]
Erythromycin Estolate	Adverse Reaction Series Leaflet No.10 [1973]
Etodolac [Lodine, Ramodar]	Current Problems No.20 [1987]
Etomidate [Hypnomidate for Infusion]	Dear Doctor Letter [1 June 1983]; Dear Doctor Letter [20 June 1983]
Felbinac [Traxam]	Current Problems No.27 [1989]
Fenbufen [Lederfen]	Current Problems No.23 [1988]; Current Problems No.24 [1989]
Fenclofenac [Flenac]	Annual Report [1984]
Fenfluramine [Ponderax]	Current Problems No.34 [1992]; Current Problems in Pharmacovigilance [June 1993]; Current Problems in Pharmacovigilance [February 1997]
Fenoterol [Berotec]	Annual Report [1990]; Current Problems No.31 [1991]
Finasteride [Proscar]	Current Problems in Pharmacovigilance [February 1995]
Flecainide [Tambocor]	Current Problems No.27 [1989]; Current Problems No.31 [1991]
Flosequinan [Manoplax]	Annual Report [1993]
Flucloxacillin	Current Problems No.35 [1992]
Fluorescein	Current Problems No.12 [1983]
Fluoxetine [Prozac]	Current Problems No.26 [1989]; Current Problems No.34 [1992]; Current Problems in Pharmacovigilance [May 1994]
Flupenthixol deconate	Current Problems No.18 [1986]
Fluvoxamine [Faverin]	Current Problems No.22 [1988]; Current Problems No.26 [1989]; Current Problems No.34 [1992]; Current Problems in Pharmacovigilance [August 1994]
Griseofulvin	Current Problems No.16 [1986]; Current Problems in Pharmacovigilance [July 1996]
Halofantrine [Halfan]	Current Problems in Pharmacovigilance [May 1994]
Haloperidol	Current Problems No.18 [1986]
Halothane	Dear Doctor Letter [1974]; Annual Report [1976]; Annual Report [1978]; Current Problems No.18 [1986]; Current Problems in Pharmacovigilance [May 1997]

Heparin	Current Problems No.28 [1990]
Hepatitis A Vaccine	Current Problems in Pharmacovigilance [November 1994]
Hexachlorophane	Annual Report [1972]
Hormonal Pregnancy Tests	Adverse Reactions Series No.13 [1975]; Adverse Reactions Series No.14 [1977]; Annual Report [1978]
Hormone Replacement Therapy	Current Problems in Pharmacovigilance [October 1996]
Hydralazine [Apresoline]	Current Problems No.14 [1985]
Hydrofluoroalkanes	Current Problems in Pharmacovigilance [February 1995]
Ibuprofen	Current Problems No.11 [1983]
Indomethacin	Annual Report [1977]
Indomethacin [Osmosin]	Current Problems No.11 [1983]
Indoprofen [Flosint]	Annual Report [1983]; Annual Report [1984]; Annual Report [1985]
Insulin	Annual Report [1975]; Current Problems No.2 [1976]; Current Problems No.29 [1990]; Annual Report [1992]
Intravenous Nutrition Solutions	Current Problems No.4 [1979]
Ipratropium Bromide [Atrovent Nebulizer Solution]	Current Problems No.13 [1984]
Isoniazid	Current Problems in Pharmacovigilance [February 1993]
Isotretinoin [Roaccutane]	Current Problems No.12 [1983]
Ketamine [Ketalar]	Current Problems No.2 [1976]
Ketoconazole [Nizoral]	Adverse Reactions Series Leaflet No.19 [1985]; Current Problems No.10 [1983]; Current Problems No.13 [1984]
Ketorolac [Toradol]	Current Problems in Pharmacovigilance [June 1993]; Annual Report [1994]
L-Tryptophan [Pacitron and Optimax]	Current Problems No.27 [1989]; Current Problems No.29 [1990]; Dear Doctor Letter [12 April 1990]; Current Problems in Pharmacovigilance [February 1994]
Labetalol	Annual Report [1978]
Lamotrigine [Lamictal]	Current Problems in Pharmacovigilance [February 1993]; Current Problems in Pharmacovigilance [October 1996]; Current Problems in Pharmacovigilance [May 1997]

Latamoxef [Moxalactam]	Current Problems No.10 [1983]
Lincomycin [Lincocin; Mycivin]	Current Problems No.2 [1976]; Adverse Reactions Series No.17 [1979]
Lipid-lowering drugs	Current Problems in Pharmacovigilance [February 1995]
Liquid Paraffin	Current Problems No.28 [1990]
Lofepramine [Gamanil]	Current Problems No.23 [1988]; Current Problems in Pharmacovigilance [May 1994]
Macleans Sensitive Teeth Formula	Current Problems No.13 [1984]
Maprotiline [Ludiomil]	Current Problems No.2 [1976]; Current Problems No.15 [1985]
Measles Rubella Vaccine	Current Problems in Pharmacovigilance [November 1995]
Mefloquine [Lariam]	Current Problems in Pharmacovigilance [July 1996]
Mebhydrolin [Fabahistin]	Current Problems No.7 [1981]
Megestrol Acetate	Annual Report [1975]
Mesalazine [Asacol]	Current Problems No.30 [1990] and Current Problems in Pharmacovigilance [July 1995]
Methyl Dopa	Current Problems No.3 [1978]
Metipranolol [Glauline]	Current Problems No.29 [1990]
Metoclopramide	Current Problems No.1 [1975]; Current Problems No.3 [1978]
Metolazone [Xuret and Metenix5]	Current Problems in Pharmacovigilance [July 1996]
Mianserin [Bolvidon, Norval]	Current Problems No.7 [1981]; Current Problems No.8 [1982]; Current Problems No.10 [1983]; Current Problems No.15 [1985]; Current Problems No.25 [1989]
Midazolam [Hypnovel]	Current Problems No.14 [1985]
Misoprostol [Cytotec]	Current Problems No.27 [1989]
Naftidrofuryl infusion [Praxilene Forte]	Current Problems in Pharmacovigilance [February 1995]; Current Problems in Pharmacovigilance [July 1995]
Naloxone	Current Problems in Pharmacovigilance [May 1997]
Nebuliser Solutions	Current Problems No.22 [1988]

Nefopam Hydrochloride [Acupan]	Current Problems No.24 [1989]
Neomycin	Adverse Reaction Series Leaflet No.14 [1977]
Neuroleptic drugs	Current Problems in Pharmacovigilance [May 1994]
Nifedipine [Adalat]	Current Problems No.4 [1979]; Current Problems No.17 [1986]
Nitric Oxide	Current Problems in Pharmacovigilance [July 1996]
Nitrofurantoin	Current Problems No.3 [1978]
Nomifensine	Current Problems No.15 [1985]
Non-steroidal anti-inflammatory agents	Current Problems No.1 [1975]; Annual Report [1985]; Current Problems No.16 [1986]; Current Problems No.17 [1986]; Current Problems No.20 [1987]; Current Problems No.32 [1992]; Current Problems in Pharmacovigilance [June 1993]; Current Problems in Pharmacovigilance [August 1994]
Noradrenaline	Annual Report [1972]; Dear Doctor Letter [May 1973]
Norfloxacin [Utinor]	Current Problems No.32 [1992]
Ofloxacin [Taravid]	Current Problems No.32 [1992]
Oil-based vaginal and rectal medications	Current Problems No.23 [1988]
Omeprazole [Losec]	Current Problems No.31 [1991]
Oral Contraceptives	Annual Report [1972]; Dear Doctor Letter [May 1973]; Annual Report [1975]; Annual Report [1976]; Current Problems No.2 [1976]; Dear Doctor Letter [1977]; Dear Doctor Letter [1983]; Annual Report [1985]; Annual Report [1986]; Annual Report [1987]; Current Problems No.21 [1988]; Current Problems No.26 [1989]; Dear Doctor Letter [1995]; Annual Report [1996]
Oxyphenbutazone	Annual Report [1977]; Dear Doctor Letter [7 March 1984]
Oxyphenisatin Acetate	Annual Report [1972]
Pancreatin preparations	Annual Report [1993]; Current Problems in Pharmacovigilance [November 1994]; Current Problems in Pharmacovigilance [November 1995]
Papaveretum	Current Problems No.31 [1991]; Current Problems in Pharmacovigilance [November 1993]
Paracetamol	Current Problems in Pharmacovigilance [November 1995]
Paraformaldehyde	Current Problems No.20 [1987]
Parentrovite [Bencard]	Current Problems No.24 [1989]
Paroxetine [Seroxat]	Current Problems in Pharmacovigilance [February 1993]; Current Problems in Pharmacovigilance [May 1994]

Perhexiline Maleate [Pexid]	Adverse Reaction Series Leaflet No.15 [1977]; Current Problems No.11 [1983]
Pertussis vaccine	Annual Report [1977]; Annual Report [1978]; Annual Report [1979]; Annual Report [1980]; Annual Report [1981]
Phenacetin	Annual Report [1974]
Phenformin [Dibotin; Meltrol; Dipar]	Current Problems No.2 [1976]; Dear Doctor Letter [1977]
Phentermine [Ionamin and Duromine]	Current Problems in Pharmacovigilance [February 1997]
Phenylbutazone	Annual Report [1977]; Dear Doctor Letter [7 March 1984]
Pimozide [Orap}	Current Problems No.29 [1990]; Current Problems in Pharmacovigilance [February 1995]
Piroxicam [Feldene]	Current Problems No.8 [1982]
Pivmecillinam [Selexid]	Current Problems No.19 [1987]
Polyethoxylated Castor Oils [Cremophor EL]	Current Problems No.10 [1983]; Current Problems No.12 [1983]
Post-coital contraception	Annual Report [1983]
Practolol [Eraldin]	Adverse Reactions Series No.11 [1975]; Current Problems No.1 [1975]; Current Problems No.2 [1976]; Current Problems No.4 [1979]
Prazosin [Hypovase]	Adverse Reactions Series Leaflet No.12 [1975]; Current Problems No.1 [1975]
Progesterone suppositories [Cyclogest]	Current Problems No.15 [1985]
Propafenone	Current Problems No.29 [1990]
Propanidid [Epontol]	Current Problems No.2 [1976]
Propofol [Diprivan]	Current Problems No.20 [1987]; Current Problems No.26 [1989]; Current Problems No.34 [1992]; Current Problems No.35 [1992]
Prostaglandin E2 [Propess]	Current Problems No.29 [1990]
Pyrazinamide	Current Problems in Pharmacovigilance [February 1993]
Pyrimethamine and Dapsone [Maloprim]	Current Problems No.13 [1984]; Current Problems No.14 [1985]
Pyrimethamine and sulfadoxine [Fansidar]	Current Problems No.15 [1985]

Quinidine [Kinidin, Kiditard]	Current Problems No.8 [1982]
Quinolones	Annual Report [1991]; Annual Report [1992]; Current Problems in Pharmacovigilance [February 1993]; Current Problems in Pharmacovigilance [July 1995]
Remoxipride [Roxiam]	Current Problems in Pharmacovigilance [November 1993]
Reserpine	Annual Report [1974]
Rifabutin [Mycobutin]	Current Problems in Pharmacovigilance [February 1994]
Rifampicin	Current Problems in Pharmacovigilance [February 1993]
Ritodrine	Annual Report [1992]; Current Problems in Pharmacovigilance [July 1995]
Salmeterol [Serevent]	Current Problems No.31 [1991]
Simvastin [Zocor]	Current Problems No.33 [1992]
Sodium Cromoglycate [Intal]	Current Problems No.6 [1981]
Sodium Fusidate [Fucidin]	Current Problems No.16 [1986]
Sodium Valproate [Epilim]	Current Problems No.6 [1981]; Current Problems No.9 [1983]; Current Problems in Pharmacovigilance [June 1993]
Sotalol [Sotacor; Beta-Cardone]	Current Problems in Pharmacovigilance [July 1996]
Spironolactone	Current Problems No.21 [1988]
Stilboestrol	Dear Doctor Letter [May 1973]
Sulphasalazine [Salazopyrin]	Current Problems in Pharmacovigilance [June 1993]
Sumatriptan [Imigran]	Current Problems No.34 [1992]
Tacrolimus [Prograf]	Current Problems in Pharmacovigilance [July 1995]
Tamoxifen	Current Problems No.26 [1989]; Current Problems in Pharmacovigilance [November 1994]
Terbinafine [Lamisil]	Current Problems No.35 [1992]
Terfenadine	Current Problems No.35 [1992]; Annual Report [1994]; Current Problems in Pharmacovigilance [February 1997]; Dear Doctor Letter [1997]
Terodiline [Micturin]	Dear Doctor Letter [25 July 1991]; Current Problems No.32 [1991]
Tetracosactrin	Current Problems No.1 [1975]
Tetracyclines	Current Problems No.23 [1988]
Thalidomide	Current Problems in Pharmacovigilance [May 1994]

Thymoxamine [Opilon]	Current Problems in Pharmacovigilance [November 1993]
Thyroxine Tablets BP	Current Problems No.5 [1981]
Tiaprofenic Acid [Surgam]	Current Problems in Pharmacovigilance [August 1994]
Tibolone [Livial]	Current Problems No.34 [1992]; Current Problems in Pharmacovigilance [November 1994]
Ticlopidine	Current Problems in Pharmacovigilance [February 1997]
Timolol Eye Drops [Timoptol]	Current Problems No.6 [1981]
Tramadol [Zydol, Tramake and Zamadol]	Current Problems in Pharmacovigilance [February 1995]; Current Problems in Pharmacovigilance [October 1996]
Trazodone [Molipaxin]	Current Problems No.13 [1984]
Triazolam [Halcion and generic preparations]	Dear Doctor Letter [1 October 1991]; Current Problems No.5 [1981]
Tricyclic Antidepressants	Current Problems No.3 [1978]
Trimethoprim	Current Problems No.15 [1985]
Vasopressin [Desmospray, Desmotabs and DDAVP tablets]	Current Problems in Pharmacovigilance [March 1996]
Vinblastine	Current Problems No.30 [1990]
Vincristine	Current Problems No.30 [1990]
Vitamin A	Current Problems No.3 [1978]; Annual Report [1990]
Warfarin	Annual Report [1987]; Current Problems No.26 [1989]
Xamoterol [Corwin]	Annual Report [1989]; Current Problems No.28 [1990]
Xanthine	Current Problems No.28 [1990]
Zimeldine [Zelmid]	Current Problems No.11 [1983]
Zomepirac [Zomax]	Annual Report [1983]
Zopiclone [Zimovane]	Current Problems No.30 [1990]
Zuclopenthixol [Clopixol and Clopixol Acubase]	Current Problems in Pharmacovigilance [July 1996]

Appendix XXX

Variations to Medicinal Products as recommended by the CSM (1995 - 1997)[289]

[289] Information taken from the Annual Reports of the CSM (Medicines Commission et al (1996) and (1997)) and Current Problems in Pharmacovigilance (MCA/CSM (1997)).

Alendronate sodium (Fosamax) *Oesophageal reactions*	Warnings on adverse reactions and information on how they could be avoided to be strengthened in the product information.
Amiodarone *Serious adverse reactions affecting the lung, liver, nervous system, eye, thyroid gland and skin.*	Product information to be updated.
Aspirin *Accidental and suicidal deaths*	Pack size restriction and label warnings to reduce risk from overdose.
Cisapride (Prepulsid, Alimix) *Serious ventricular arrhythmias*	Co-administration with antifungals, itraconazole, miconazole, ketoconazole, fluconazole, erythromycin and clarithromycin to be contra-indicated.
Co-amoxiclav (Augmentin) *Cholestatic jaundice*	Product information amended to reflect revised indications.
Hormone Replacement Therapy *Deep vein thrombosis*	Information leaflet prepared for patients and product information to incorporate warnings.
Indinavir (Crixivan) *Formation of renal stones, hyperbilirubinaemia, taste disturbance and dry skin*	Warning to be added to the product information
Lipid lowering agents *Myopathy, myositis and rhabdomyolysis*	Product information to contain appropriate warnings and patients using combinations of lipid-lowering drugs should be monitored.
Mefloquine (Lariam) *Neuropsychiatric adverse reactions*	Existing warnings in the product information to be strengthened.
Mesalazine *Serious and fatal reports of blood disorders*	Product information to be revised.
Methotrexate *Serious and sometimes fatal blood dyscrasias*	Monitoring of full blood count, liver and renal function during low dose therapy recommended.
Oral contraceptives *Venous thromboembolism*	Change in recommendations so that only women who are intolerant of other combined oral contraceptives should take oral contraceptives containing gestodene and desogestrel
Oral contraceptives *Breastcancer*	Warnings in product literature to be amended to reflect new evidence that possible increased risk is greatest for older women.

Paracetamol *Accidental and suicidal deaths*	Pack size restriction and label warnings to reduce risk from overdose.
Pimozide (Orap) *Serious and fatal ventricular arrhythmias*	ECG monitoring to be performed annually, changes to product information and certain specified medicines to be avoided.
Quinolone antibiotics *Damage including rupture to tendons*	Product information for patients and doctors to contain appropriate warnings.
Sotalol (Sotocur, Beta-Cardone) *Higher mortality rate than other treatments*	Limited to the treatment of cardiac arrhythmias.
Tacrolimus (Prograf) *Hypertrophic cardiomyopathy*	Warnings to be added to the product information advising echocardiographic monitoring and dose reduction should abnormalities develop.
Terfenadine *Cardiac arrhythmias*	Change in status to being available on prescription only. These step taken despite steps having been taken to introduce effective safeguards through warnings and precautions in product information
Tramadol (Zydol, Tramake, Zamadol) *Dependence, withdrawal reactions, convulsions and allergic reactions*	Warnings in the product information to be strengthened.

Appendix XXXI

Medicinal Products which have been withdrawn for safety reasons (1961 - 1997)

Each entry is set out as follows:

Generic name (Proprietary name) [Manufacturer] LEGAL CLASSIFICATION	When licensed or introduced. Uses. *Adverse reactions of particularconcern.* Date of withdrawal.

Alclofenac (Prinalgin) [Berk Pharmaceuticals Ltd)] POM	Licensed in 1972. A non-steroidal anti-inflammatory drug used in the treatment of arthritis. *Rash and death.* Withdrawn in 1979.
Benoxaprofen (Opren) [Lilly Industries Ltd (Dista Products Ltd)] POM	Licensed in 1980. Another non-steroidal anti-inflammatory drug. *Photosensitivity, gastrointestinal bleeding, serious liver and kidney damage, and death.* Withdrawn in 1982 .
Clioquinol (Entero-Vioform) [Ciba-Geigy] P	Introduced in 1930. Used in the treatment and prevention of "travellers' diarrhoea". *Subacute myelo-optic neuropathy (SMON).* Withdrawn in 1981.
Dalkon Shield [A.H. Robins] POM	Introduced in 1971. An intrauterine contraceptive device. *Pelvic inflammatory disease, septic abortion, infertility and death.* Withdrawn in 1975.
Debendox, known as Bendectin in the US) [Merrell Dow]	Introduced in 1958. An antiemetic drug used in pregnancy. *Alleged birth defects.* Withdrawn in 1983.
Dexfenfluramine (Adifax) [Servier] POM	Used in the treatment of obesity. Risk of developing mitral, aortic, tricupsid or mixed valve incompetence (valvular heart disease). Withdrawn in 1997

Table x contd.

Diethylstilboestrol (DES) (various) [Various manufacturers] POM	First described in 1938. A synthetic non-steroidal oestrogen used for preventing miscarriages and preterm births. *Vaginal adenocarcinoma.* Withdrawn in 1973.
Fenclofenac (Flenac) [Reckitt & Coleman] POM	Licensed in 1978. A non-steroidal anti-inflammatory drug used in the treatment of arthritis. *Skin rashes, impaired kidney and liver function, and death.* Withdrawn in 1984.
Fenfluramine (Ponderax) [Servier] POM	Used in the treatment of obesity. Risk of developing mitral, aortic, tricupsid or mixed valve incompetence (valvular heart disease). Withdrawn in 1997.
Feprazone (Methrazone) [WB Pharmaceuticals] POM	Licensed in 1978. A non-steroidal anti-inflammatory drug used in the treatment of arthritis. *Gastrointestinal reactions and death.* Withdrawn in 1984.
Flosequinan (Manoplax) [Boots] POM	Licensed in 1992. A vasodilator used in the treatment of heart failure. *Death.* Withdrawn in 1993.

Indomethacin (Osmosin) [Merck, Sharp & Dohme] POM	Licensed in 1982. A sustained release formulation of the non-steroidal anti-inflammatory drug, indomethacin, used in the treatment of arthritis. *Intestinal perforation.* Withdrawn in 1984.
Indoprofen (Flosint) [Farmitalia Carlo Erba Ltd] POM	Licensed in 1982. A non-steroidal anti-inflammatory drug used in the treatment of arthritis. *Gastrointestinal adverse reactions.* Withdrawn in 1985.
Iophendylate (Myodil) [Glaxo] POM	Introduced in 1945. A spinal X-ray imaging agent. *Arachnoiditis.* Withdrawn in 1987.
L-Tryptophan (Pacitron and Optimax) [Rorer; E. Merck] POM	Used in the treatment of depression. *Eosinophilia-Myalgia Syndrome.* Withdrawn in 1990.
Metipranolol (Glauline) [Smith & Nephew) POM	An ophthalmic ß-blocking agent used in the treatment of chronic open angle glaucoma. *Granulomatous anterior uveitis.* Withdrawn in 1990.
MMR Vaccine (Pluserix-MMR; Immravax) [SmithKline Beecham and Merieux] POM	Licensed in 1988. Measles, mumps and rubella vaccine. *Meningitis.* Withdrawn in 1992.
Naftidrofuryl (Praxilene Forte) [Lipha Pharmaceuticals Ltd] POM	Used in the treatment of peripheral vascular disease. *Serious adverse reactions and fatalities.* Parenteral naftidrofuryl withdrawn in 1995
Nomifensine (Merital) [Hoechst] POM	Licensed in 1976 and used in the treatment of depression. *Haemolytic anaemia.* Withdrawn in 1986.
Oral Contraceptives (various) [Various manufacturers] POM	Introduced in 1960. *Thrombosis.*
Oxyphenbutazone (Tandacote, Tanderil) [Ciba-Geigy] POM	Introduced in 1965. A non-steroidal anti-inflammatory drug. *Blood dyscrasias.* Withdrawn in 1984.
Pemoline (Volital) [Laboratories for Applied Biology Ltd] POM	Used in the treatment of hyperkinetic syndrome. *Serious hepatic reactions leading to liver transplantation or death.* Withdrawn in 1997.
Polidexide (Secholex) [Pharmacia (Great Britain) Ltd] POM	Licensed in 1974. Mutagenic contaminant in drug substance.

Practolol (Eraldin) [ICI] POM	Introduced in 1970. A ß-adrenergic blocking agent used in the treatment of cardiovascular disease. *Sclerosing peritonitis and oculomucocutaneous syndrome*. Withdrawn in 1975.
Prostaglandin E2 (Propess) [Roussel] POM	Licensed in 1989. A controlled release pessary for cervical ripening in the induction of labour. *Uterine hypertonus and foetal distress*. Withdrawn in 1990.
Suprofen (Suprol) [Ortho-Cilag Pharmaceutical] POM	Licensed in 1983. A non-steroidal anti-inflammatory drug used in the treatment of arthritis. *Gastrointestinal adverse reactions*. Withdrawn in 1986.
Temafloxacin (Teflox) [Abbott] POM	Licensed in 1991. An oral quinolone antibiotic promoted for use in vulnerable groups such as the elderly or patients with underlying disease. *Hypoglycaemia, hepatic dysfunction, haemolytic anaemia, renal dysfunction, anaphylaxis and death.* Withdrawn in 1993.
Terodiline (Micturin) [Kabi Pharmacia Ltd] POM	Licensed in 1986 for the treatment of urinary incontinence. *Ventriculartachycardia*. Withdrawn in 1991.
Triazolam (Halcion) [Upjohn) POM	Licensed in 1979. A benzodiazepine which had a higher frequency of *reversible psychiatric side-effects, particularly loss of memory and depression* than other benzodiazepines, and also the risk of rare idiosyncratic episodes of violence. Withdrawn in 1991.
Zimeldine (Zelmid) [Astra] POM	Licensed in 1982 for the treatment of depression. *Guillan-Barré Syndrome*. Withdrawn in 1983.
Zomepirac (Zomax) [Ortho-Cilag Pharmaceutical] POM	Licensed in 1981. A non-steroidal anti-inflammatory drug. *Anaphylactic shock; renal failure*. Withdrawn in 1983.