EVALUATING PHARMACEUTICAL EXTERNAL REFERENCE PRICING REGULATION IN EU: A HYBRID RESOURCE / AGENT MODELLING AND SIMULATION APPROACH

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Declaration

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Chapter 7 final draft of this PhD thesis, includes text and figures from a published journal paper* coauthored with professor Susan Howick (SH) and professor Alec Morton (AM) (Kazakov et al., 2021), with the exception of Figures 7.2.1, 7.2.2, 7.2.3, 7.2.4, 7.2.7, 7.2.8 and 7.3.1 and the text associated with those figures (Table A).

Parts of Chapter 6 includes tables from the above published paper (Table 6.1.A, Table 6.1.B and Table 6.1.C in section 6)

Parts of Chapter 10 includes text from the above published journal paper (specifically from section 11 of the paper).

Paper (Chapter or section)	PhD Thesis author	Co-authors
Chapter 7 (whole chapter contents without figures 7.2.1 to 7.2.4, figures 7.2.7 to 7.2.8 and Figure 7.3.1)	Designed and conducted the analysis Drafted the paper and led the submission and revision process for journal publication	Supervised the analysis, commented and suggested changes to the draft paper: SH and AM
Chapter 6, section 6.1		
Chapter 10, parts of section 10.1		

Rossen M. Kazakov

Date:

* R. Kazakov, S. Howick and A. Morton, Managing complex adaptive systems: A resource/agent qualitative modelling perspective, European Journal of Operational Research, https://doi.org/10.1016/j.ejor.2020.08.007

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To my family and our cat,
who supported me in my efforts
to prove that management
science can bring meaningful
contribution to policy decision
making & systems improvement

R. Katz

Table of Contents

List of Abbreviations

ABM Agent-based Modelling

AbM Agent Behaviour Maps

AiM Agent Interaction Maps

AST Anticipatory Systems Theory

Avg Average

BDT Behavioural decision Theory

CAS Complex Adaptive Systems

CR Critical Realism

DCR Dialectical Critical Realism

DE Discrete Event

ERP External Reference Pricing

EURIPID European Commission Grant for Project "Statistical data for medicinal product pricing"

INN International Nonproprietary Name

IRP Internal Reference Pricing

MEPD Market entry price discount

Min Minimum

PT Parallel Trade

RAM Resource Agent Maps

RBT Resource – based Theory

RQ Research Question

RDT Resource Dependence Theory

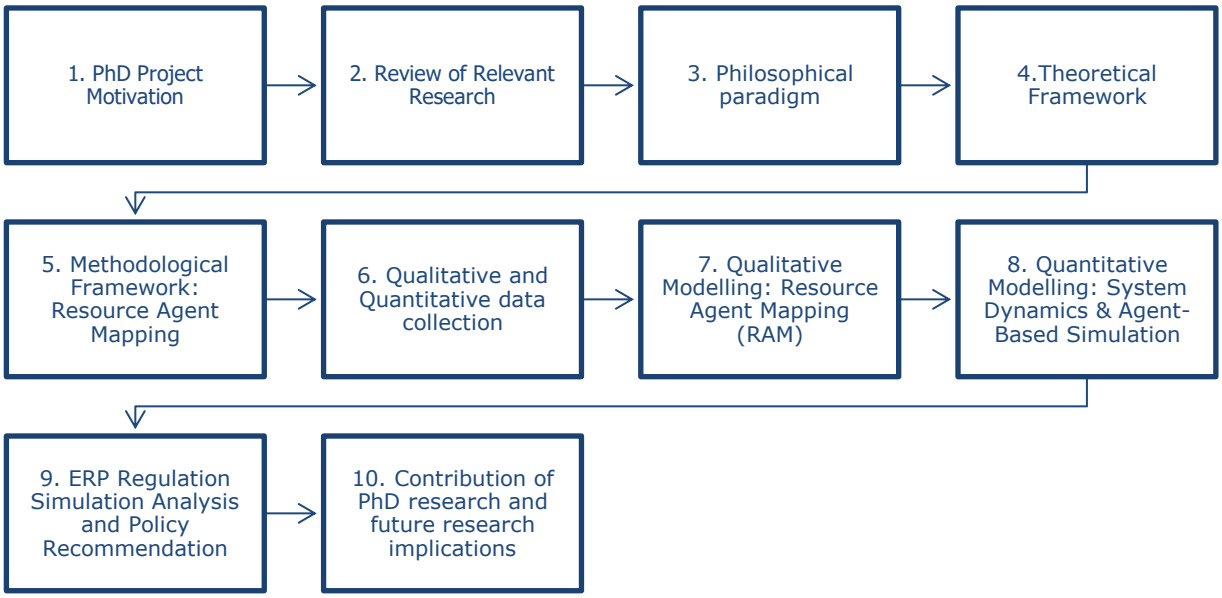
RM Resource Maps

SD System Dynamics

List of Tables

List of Figures

Chapter Roadmap



Abstract

The aim of this research is to evaluate the impact of the pharmaceutical pricing regulation in the EU in relation to drugs access, affordability and availability. It aligns with the call of the Council of the European Union (2016) and corresponds also to the call regarding the need for use of dynamic simulation methods for the analysis of healthcare system interventions (Roberts 2015). The methodological approach of my research is related to application of a hybrid qualitative and quantitative system dynamics and agent-based simulation modelling. This approach is employed for the evaluation of the External Reference Pricing (ERP) regulation effect on equitable access, availability, and affordability of drugs on the cardiovascular pharmaceutical market in EU. The research is nested in a rich theoretical paradigm, capable of supporting the hybrid simulation modelling approach. This paradigm integrates the Resource-dependence Theory and Resource-based Theory, Behavioural Decision Theory, and Anticipatory Systems Theory. It fills practical, methodological and theoretical gaps in relation to the research topic.

My PhD's main contribution is connected to both methodological and practical aspects of developing a novel problem structuring method, Resource Agent Maps (RAM), and using that method for qualitative analysis and as a conceptual validation and hybridization procedure for designing a hybrid simulation evaluation of the ERP regulation effects. The ERP analysis demonstrates that applying a RAM approach can enable a comprehensive evaluation (taking account of both resource-feedback and agent-based perspectives) of the ERP effect on drug equitable access, affordability and availability. In addition, the analysis extends previous research on the ERP, helping to overcome previous limitations (Toumi et al., 2014, Vogler et al. 2015).

Main insights from the ERP regulation evaluation are that the ERP alone has no effect on drug access delay (access criterion). On the contrary, it provides an attractive route for propagation of the highest price at the first country of launch to other referencing countries. Other factors like mandatory official price discounts can have effects on delays in local markets, which could interfere with the ERP tool set of rules. Also, ERP alone has no price decrease (affordability criterion) effect for on patent drugs or any drug in a monopolistic market. Price decrease is an effect mainly from local price competition intensity, which the ERP regulation transfers to other reference basket countries, depending on reference price calculation formula and reference country basket composition. ERP can have effect on drug market exits (availability criterion) for off patent innovative and generic medicines, depending on pharmaceutical firms' pricing strategies and on the indirect effects of price competition, local prescribing regulation and parallel trade.

Chapter 1 PhD Project Motivation, Research Question and Context

1.1 Motivation for the research

The External Reference Pricing (ERP) practice is spread among almost all European countries. Figure 1.1.1 and Figure 1.1.2 show how much this pricing policy is prevalent across Europe (Vogler, 2019; Kanavos et al., 2010; Remusat et al., 2015).

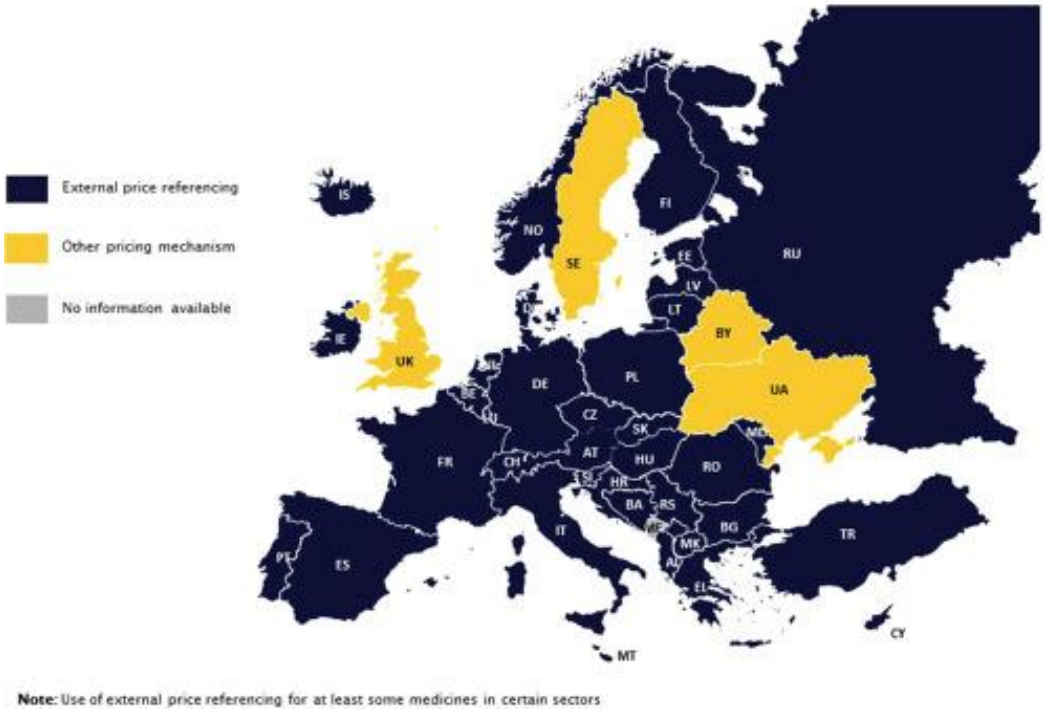
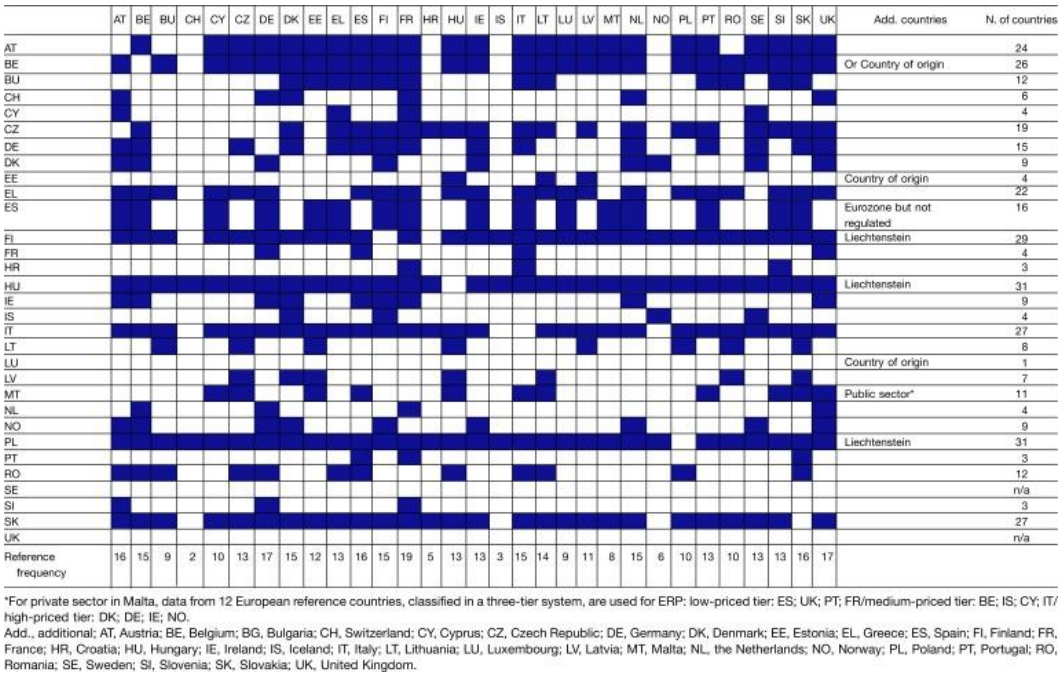


Figure 1.1.1 Prevalence of the ERP regulation in European countries (blue colour)



*For private sector in Malta, data from 12 European reference countries, classified in a three-tier system, are used for ERP: low-priced tier: ES; UK; PT; FR/medium-priced tier: BE; IS; CY; IT/ high-priced tier: DK; DE; IE; NO.
Add., additional; AT, Austria; BE, Belgium; BG, Bulgaria; CH, Switzerland; CY, Cyprus; CZ, Czech Republic; DE, Germany; DK, Denmark; EE, Estonia; EL, Greece; ES, Spain; FI, Finland; FR, France; HR, Croatia; HU, Hungary; IE, Ireland; IS, Iceland; IT, Italy; LT, Lithuania; LU, Luxembourg; LV, Latvia; MT, Malta; NL, the Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; SE, Sweden; SI, Slovenia; SK, Slovakia; UK, United Kingdom.

Figure 1.1.2 ERP regulation 'reference baskets' (ERP drug price comparison among different EU states)

ERP is a pan European practice which is applied by national authorities to benchmark a medicine price among a group or a "basket" of a different number of European Union member markets. It appears to be controversial in relation to its effect on medicine access, affordability and availability (Vogler et al. 2016; Vogler et al. 2014; Vogler & Paterson 2017; Rémuzat et al. 2015; Wouters 2013; Council of the European Union 2016) and containing important challenges like price calculation formula, reference countries choice variation, and confidential (not transparent) pricing. (Schneider 2017) . The global systemic complexity of ERP and the limited evaluation of its effect on the pharmaceutical systems (Toumi et al. 2014; Thivolet 2014) make it a choice for a fruitful exploration by hybrid modelling and simulation approach, relevant to the call of Roberts that 'dynamic simulations in health care had come of age' (Roberts 2015).

In relation to the ERP regulation challenges an EU initiative was set up called EURIPID, following the European Commission Grant "Statistical data for medicinal product pricing" under the call HP-PJ-2014 (No. 664317). The grant was awarded to a consortium of five institutions from Austria, Czech Republic (2), Hungary and Sweden, which form the EURIPID Collaboration. The overall objective of the grant was to develop a guidance document on a "coordinated approach of national authorities regarding the use of external reference pricing to avoid/mitigate negative impact for patient access to medicines" (Schneider and Habl, 2017) .

This initiative brought together different stakeholders including Medicines of Europe (MfE) and EFPIA (the European Federation of the Pharmaceutical Innovation Association), which argued that ERP could lead to contradictory outcomes due to hindering product availability, affordability and access to market. In March 2017 and March 2018, a best practice report by the EURIPID (Schneider and Habl, 2017) and guidance document report on ERP (Hable 2018), were issued after a number of working group meetings starting in 2015 and 2016, 2017 and 2018 between the EURIPID consortium and the EU pharmaceutical associations. Among the main challenges of the ERP regulation explained further in the next chapter, a key question appeared to be the lack of sufficient analyses and evidence related to the comprehensive evaluation of the ERP regulation effect on equitable access, affordability, and availability of medicines in practice.

1.2 Aim of the research

The aim of this PhD research is to apply multimethodological approach in modelling and simulation for the evaluation of the External Reference Pricing (ERP) in EU.

My intention to explore the ERP regulation effects came out from the EURIPID key challenges and the Council of the EU conclusions. It is related to designing an interactive modelling and simulation learning environment for policy evaluation by applying a multimethodology (Mingers 2001; Howick & Ackermann 2011; Marshall, Burgos-Liz, et al. 2015; Balaban et al 2015; Balaban et al. 2014; Djanatliev & German 2016) approach integrating system dynamics (SD) and agent based (AB) qualitative and quantitative modelling and simulation in one framework.

Ideally a hybrid SD/AB modelling and simulation approach for evaluation of the ERP effects on the pharmaceutical market system, would be capable for revealing market dynamics and hidden dialectical interrelations, which are coming out of resources and agents complex adaptive behaviour. It can help the exploration of ERP what-if scenarios and their effect on agent competitive behaviour, limited resource utilization, supply and demand dynamics and market imperfections.

The aim of my PhD research will be to fill a threefold gap related to:

- Practical aspect: Application of hybrid modelling and simulation to pharmaceutical pricing policy and regulation for evaluating ERP policy and regulation effect on the pharmaceutical market (Schneider 2017; Hable 2018; Council of the European Union 2016)

- Theoretical aspect: Borrowing and developing theory to support the SD/AB integration (Ackermann et al. 2014)
- Methodological aspect: Developing a procedure for integrating qualitative and quantitative SD and AB modelling and simulation (Howick et al. 2008; Ackermann et al. 2014)

1.3 Research Question

My project will concentrate on the following Research question: "What are the effects of the ERP regulation on EU pharmaceutical market systems in relation to equitable access to, availability and affordability of medicines? What theoretical and methodological frameworks can provide means for the appropriate exploration of those effects?"

The exploration of the RQ will focus on the following outcome criteria:

- ERP effect on time delay in launching medicines (drug access criterion)
- ERP effect on excessive pricing of medicines (drug affordability criterion)
- ERP effect on shortages of Cardio Vascular Disease medicines (drug availability criterion)
- Theoretical framework, suitable to support the analysis of the above effects
- Methodological framework, suitable for the analysis of the above effects

The three main outcome criteria, related to the research question (drug access, drug availability and drug affordability) are defined through the literature reviewed on the External Reference Pricing regulation and practice in the EU (Table 2.2.1 and Vogler et al., 2015). The definition for drug access criteria is the time (respectively time delay) for a new drug (innovative on patent drug, innovative off patent drug or a new generic drug) to enter a local country market. The time to enter a local market is associated with drug delays which differs between ERP local markets, as they occur due to regulatory, administrative or commercial reasons. Drug availability criterion is defined in the literature as the presence of a drug on a local market throughout the drug supply chain. Hence, this criterion is associated with drug unavailability, which appears when a certain medicine, after being launched on a local market, is being withdrawn from that market due to regulatory, commercial or other reasons; Drug affordability criterion is defined as per the degree of how high or how low the purchase price of a drug can be, which has been officially approved by a local market pricing authority and in comparison to different prices of one and the

same medicine across ERP markets. This criterion is related to the pricing authorities social purpose to negotiate lower drug prices for new on patent, off patent or generic drugs, in order to improve their affordability to patients and government healthcare funds;

The research questions will be explored in relation only to ambulatory care and not the hospital market. In addition, only oral medicines that are not biological medicines or biosimilars are considered in the ERP simulation scenarios.

1.4 External Reference Pricing ERP Context

The ERP practice emerged well before the European Commission funded initiative in 2010 called EURIPID. This initiative is related to providing EU wide drug price information with the goal to help local pricing authorities to compare product price variation in different EU member countries. Its original aim is to aid the process of price convergence and medicines affordability across the EU.

External Reference Pricing ERP is a price control policy. It is applied by EU governments to maintain control over high drug prices by putting a pricing equality barrier obliging manufacturers to converge their product prices against their practice to exploit price discrimination by applying differential pricing across the fragmented EU country markets (Carone et al. 2014; Leopold et al. 2012; Toumi et al. 2014; Rémuzat et al. 2015; Vogler, Zimmermann, et al. 2015; Kanavos et al. 2010). However, a key consideration is that the regulators' attempt to equalize product pricing by the ERP price comparison with reference countries could have urged pharmaceutical industry to internalize the above price control practice. This could be done by maintaining differential product pricing through market price discounting of the officially approved ERP list price, in accordance with the findings of the information economics theory (Barkley Rosser Jnr 2003).

A recent efficiency report by the EURIPID initiative members outlined key points related to the ERP policy and the international price comparison practice benefits and limitations. This report is a deliverable of the European Commission Grant "Statistical data for medicinal product pricing" under the call HP-PJ-2014 (No. 664317).

For the purpose of that report, the ERP is defined as the practice of "using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country" (Schneider and Habl, 2017). The author of the report defined the rational of the ERP to

be connected to containment of pharmaceutical expenditure and to the „need to regulate the pharmaceutical markets which are imperfect due to information imperfection and if left unregulated can lead to market failure", like drug unavailability or unaffordability.

A key challenge of the ERP regulation acknowledged by the EURIPID report is the deviation of real prices from list prices:

> "Undisclosed rebates or other comparable arrangements result in inflated list prices and - as a consequence - in unreliable price benchmarks. ... However, these procedures increasingly obscure prices and bias the distribution of information in favour of the pharmaceutical manufacturer." (Schneider and Habl, 2017)

The following key considerations from the last EURIPID guiding document report (Habl, 2018) need also be taken into account for the evaluation of the ERP effect on pharmaceutical market system:

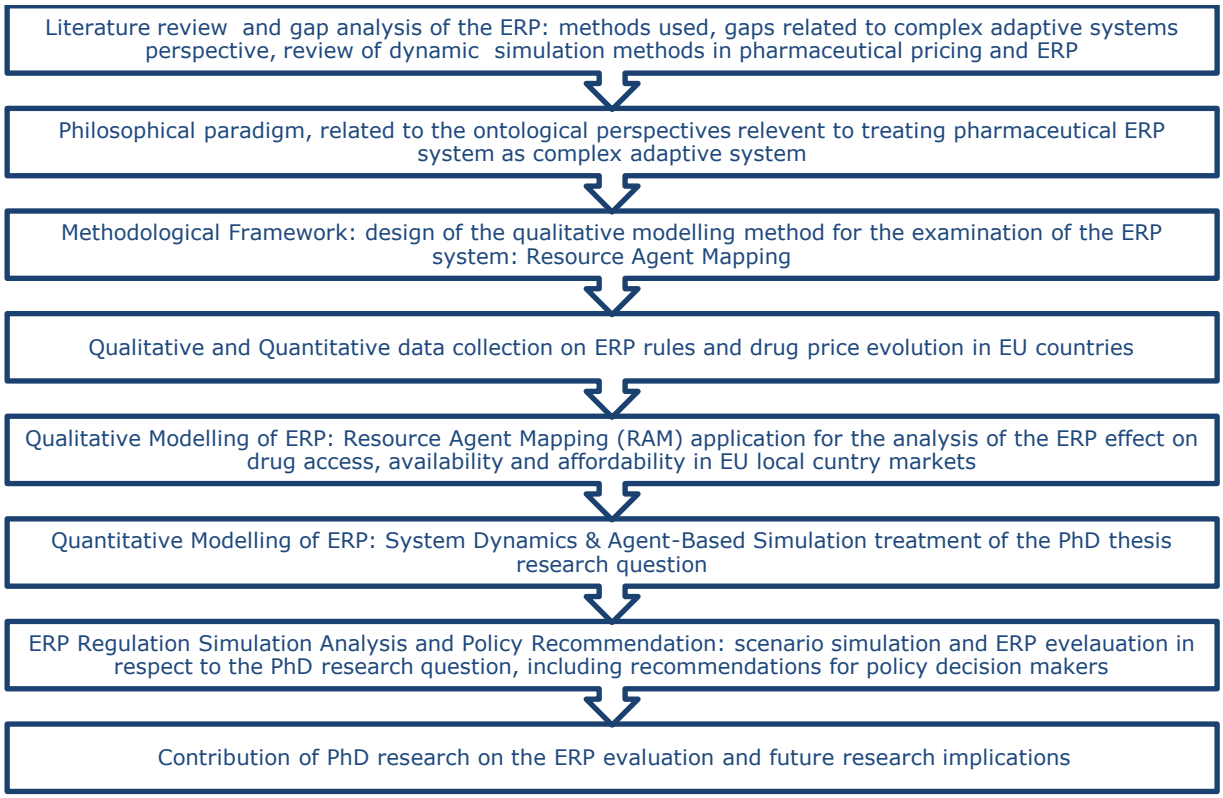
- ERP is an important policy tool that should be used in a mix with other instruments and not as stand-alone policy tool
- The aim of the national pharmaceutical policy should determine the selection of reference countries
- Evidence has shown that ERP is most effective when applied to pharmaceuticals without generic or therapeutic competition
- The pricing formula applied for ERP should reflect the national pricing policy objective

The "Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States" (Council of the European Union 2016) can provide a very appropriate and up-to-date reference point for the exploration of the ERP regulation in relation to the outcome effect on drug entry delay, high pricing and product exit out of a country market;

ERP regulation and its effect on the timely drug market access, drug affordability and drug availability, will be evaluated in accordance with key Council of EU conclusions (Table 1.4.1 in Appendix A to Chapter 1) relating to the need for analysing regulation effects on affordability of medicinal products, on market failure in EU Member States to ensure patients access to effective and affordable essential medicines for conditions that pose a high burden for patients and health systems, which is endangered by unsustainable price levels, or due to drug market exits, or due to drug entry delays to national markets.

The above considerations are connected to the sustainability of national healthcare systems, and their dependence on factors like affordability of medicinal products and possible unintended or adverse consequences of local regulation and legislative incentives, which could interfere with pricing strategies of drug companies.

PhD Thesis next steps



Chapter 2 Review of relevant research on ERP and on SD and AB modelling and simulation in pharmaceutical policy and regulation

2.1 A review of the relevant research concerning External Reference Pricing (ERP) in EU

Initially, I have conducted a narrative literature research (O'Gorman and Kevin, 2014) , with a narrow scope (Howick and Ackermann, 2011), focused on the ERP regulation context and main results of selected published articles (including their authors, ERP specific topic and methods applied), are shown in Table 2.2.1. Full list of papers is included in the Appendix A to this chapter. After that, I have conducted a gap analysis and continued with review on dynamic simulation methods in pharmaceutical regulation, and pharmaceutical pricing (Figure 2.1.1)

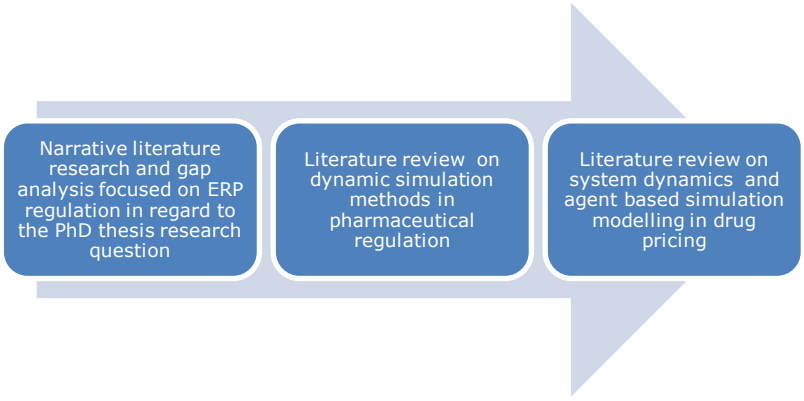


Figure 2.1.1 Literature review procedure

This literature review has had the purpose to search and reveal published papers that have presented studies on the ERP regulation in EU and its effects on the pharmaceutical market system, and mainly on the three main criteria of drug access, affordability and availability on local EU markets. This narrowed the scope of the findings and the number of the selected papers. They are included in Table 2.2.1 and categorized according to their research method and research question relevance to the above ERP effect criteria.

The WHO reviewed the ERP policy and identified potential indirect effects of ERP. These included the design and implementation of international pricing and marketing strategies by the pharmaceutical industry to counteract the effects of ERP and maximize global

profits (WHO, 2015). Another effect could be that the choice of reference countries may lead to inflated prices. If ERP is being used as the only method for price setting, entry of new products may be delayed and price manipulation may result. The report states that transaction prices are elusive – the prices that countries can access are often not real but virtual list/catalogue prices. Although there is no conclusive evidence about the impact of ERP, instances of launch delays and non-availability of new medicines in "low price" countries suggest there may be unintended negative effects. Price convergence, resulting from higher prices in lower-income countries and decreasing price transparency, is also a possible negative effect.

Persson & Jönsson (2016) analysed the effect of ERP on limitation and delay of new drug entry in the low income market, and limitation of ERP price comparison due to price differentiation tactics by drug companies. Richter (2008) applied mixed integer linear model to examine ERP national policy and parallel trade effect/implication on drug launch and pricing decisions. His findings again were related to the global pricing game that pharmaceutical firms play in order to limit and offset ERP regulation effects on lowering drug prices.

De Weerdt et al. (2015) found that for patented drugs, ERP may 'encompass the largest impact on drug shortages', i.e. drug´s availability. For generic medicines, they suggest that internal or external reference pricing, tendering, as well as price capping may affect drug shortages.

Leopold et al. (2012) studied the impact of the EPR on on-patent medicine prices by statistical analyses (multiple regression analysis). They examined these effects, adjusting for other factors such as sales volume, exchange rates, gross domestic product (GDP) per capita, total pharmaceutical expenditure, and size of the pharmaceutical industry.

Schneider et al. (2016) analysed the impact of changes in the EPR methodologies on prices scenarios (consideration of statutory discounts, regular price revisions, changes in the composition of reference countries, changes in the calculation method, changes in choice of exchange rate, and accounting for the economic situation of the reference countries) run over a 10 year horizon by the application of a variation of the DE modelling research (Toumi et al., 2014).

Souliotis et al. (2016) used non-randomized experiment to evaluate the External reference pricing (ERP) effect on market distortions and barriers to care in mostly the weak economies, ethical and political point of view and examined the influence of flexible and adaptable to health systems' affordability ERP structures.

Vogler et al. (2015) found that concerns have been voiced that medicine shortages that have increasingly been observed also in higher income countries, are, among other factors, attributable to existing pricing policies. They acknowledged that ERP policy tends to incentivize marketing authorization holders to first launch medicines in countries with higher price levels, and delay, and even refrain from, launching in low-price countries.

In another paper, Vogler et al. (2015) state that ERP incentivises the marketing authorisation holders to first launch their products in high-priced countries and to delay, or not to market, in lower-priced countries, in order not to negatively impact their reference price. Medicine shortages that have increasingly been observed in European countries in recent years might be attributable to strategic launches of the pharmaceutical industry in response to the EPR policy. Moreover, manufacturers are likely to refrain from offering lower prices to lower-income countries, and thus reduce affordable access. However, they assert that EPR can generate savings for public payers in some countries, at least in the short-term. After they used Toumi et al. (2014) DE simulations, the authors claim that savings might be higher if actual paid prices (discounted prices) were considered and regular price revisions were undertaken.

Kanavos et al. (2010) argued that EPR schemes often generate disproportionate price levels in relation to national abilities to pay due to the reliance on foreign list prices which do not reflect negotiated discounts; and those manufacturers apply launch strategies to exert upward pressure on prices.

Carone et al. (2014), Leopold et al. (2012) have contributed to the critical analysis of the ERP framework in EU by bringing in front the discussion on the pharmaceutical pricing related tactic in order to offset and even internalize the effect of the ERP regulation on drug price variation. Carone et al. (2014) argued that achieving cost-containment through ERP is limited, comparing pharmaceutical prices is difficult because published list prices may differ substantially from effective real market prices due to different pricing regimes and little price transparency; that margins for pharmacists and wholesalers and the value-added tax on pharmaceuticals differ across countries, price discounts are not public and leave listed prices unaffected. They acknowledged that drug industry adaptation strategies result in list-price inflation and cross-country convergence of prices, and that ERP can make pricing across reference countries circular.

Fontrier et al. (2019) found in their policy review that ERP appears to be associated with international implications, including spillover effects, price instability, price convergence and launch delays. However, they state that these effects cannot be solely attributed to or caused by ERP per se and there may be other factors at play, like market size and income levels (in terms of GDP per capita) of a country, exchange rate fluctuations as

well as other supply-side regulations can either trigger one or more of these effects or, reduce their impact.

Holtorf et al. (2019) made a best practices review, in which they assert that ERP scope should extend only to reimbursed single-source products (on-patent pharmaceuticals), composition of country basket should be about 5-7 countries with similar socioeconomic and HC environment, reference price calculation should be done on the average or median price of the same product, and frequency of price revisions should be yearly or biannual, including reasonable time for implementation on the market.

Maini and Pamolli, 2020 have found that the ERP practice generates an incentive for firms to withhold products from low-income countries, relevant to the drug access criterion. Using a novel moment inequality approach, they estimated a structural model to measure the extent to which ERP policies affect access to innovative drugs across Europe. According to them, the ERP regulation increased entry delays in eight low-income European countries by up to one year per drug.

Geng and Saggi, 2017, have used a game theoretic approach set for a two-country (home and foreign) model, where demand is asymmetric across countries. They showed that home's unilaterally optimal ERP policy permits the home firm to engage in a threshold level of international price discrimination above which it is (just) willing to export (relevant to the drug access criteria). If there were a price control abroad or bargains over price with the foreign government, an ERP policy could even yield higher home welfare than a direct price control.

Geng and Saggi, 2020, extended their game theoretic approach set in a two-country (home and foreign) model, to include generic competition in each market. They analyzed home's optimal policy choices regarding two major types of price regulations: external reference pricing (ERP) and direct price controls. They found that home country's nationally optimal ERP policy decreased domestic drug price while maintaining the firm's export incentive. This ERP policy resulted in a negative international price spillover that the foreign country could (partly) offset via a local price control.

Table 2.1.1 Main Results of the Literature Review on the ERP Topic, including papers exploring the ERP associated effects related to the three criteria of drug access, availability and affordability' (noted by 'yes' or 'no'), relevant to the PhD thesis research question

Publication	External Reference Pricing (ERP) Topic	Access	Affordability	Availability	Method
Vogler et al. (2015)	Study on enhanced cross-country coordination in the area of pharmaceutical product pricing. EPR has some limitations. It incentivises the marketing authorisation holders to first launch their products in high-priced countries and to delay, or not to market, in lower-priced countries, in order not to negatively impact their reference price.	Yes	Yes	Yes	Comparative analysis
Rémuzat et al. (2015)	Summarize and discuss the main findings of part of a large project conducted for the European Commission on External reference pricing discrete event simulation analysis in 31 European countries (28 EU MS, Iceland, Norway, and Switzerland)	No	Yes	No	A systematic structured literature review, with a consultation of authorities and international organisations
Thivolet et al. (2014)	Evaluation of the potential impact of the new AMNOG law (Integration of the drug price discount in				DE simulation modelling

	the public list price) in Germany, on the external reference pricing (ERP) in Europe	No	Yes	No	
Persson and Jönsson (2016)	Effect of ERP on limitation and delay of new drug entry in low income market, and limitation of differential pricing, no real prices for use in ERP systems due to price differentiation tactic	Yes	Yes	No	Comparative analysis
Richter (2008)	External reference pricing national policy and parallel trade effect/implication on drug launch and pricing decisions, global repeated pricing game	Yes	Yes	Yes	Mixed integer linear model
De Weerdt et al. (2015)	For patented drugs, external price referencing may encompass the largest impact on drug shortages. For generic medicines, internal or external reference pricing, tendering as well as price capping may affect drug shortages	No	No	Yes	Analytic comparative legal analysis
Leopold et al. (2012)	Impact of external price referencing (EPR) on on-patent medicine prices, adjusting for other factors that may affect price levels such as sales volume, exchange rates, gross domestic product (GDP) per capita, total pharmaceutical expenditure (TPE), and size of the pharmaceutical industry.	No	Yes	No	Statistical analyses (multiple regression analysis)

Schneider et al. (2017)	Impact of changes in the EPR methodologies on prices. Scenarios (consideration of statutory discounts, regular price revisions, changes in the composition of reference countries, changes in the calculation method, changes in choice of exchange rate, and accounting for the economic situation of the reference countries) run over a 10 year horizon.	No	Yes	No	Surveyed methodological specifications Discrete-event simulations
Souliotis et al. (2016)	External reference pricing (ERP) effect on market distortions and barriers to care (drug delays) in mostly the weak economies, ethical and political point of view. Examining the influence of flexible and adaptable to health systems' affordability ERP structures.	Yes	Yes	Yes	Non-randomized experiment
Vogler et al. (2015)	Medicine shortages that have increasingly been observed also in higher income countries, are, among other factors, attributable to existing pricing policies. ERP tends to incentivize marketing authorization holders to first launch medicines in countries with higher price levels, and delay, and even refrain from, launching in low-price countries.	Yes	No	Yes	Comparative analysis
Kanavos et al. (2010)	Relative merits of ERP by taking into account the views and perspectives of key stakeholders including governmental bodies, key purchasers and				Comparative analysis

	pharmaceutical manufacturers, as well as analyse market and pricing dynamics. Effects include launch tactics and price inflation.	Yes	Yes	No	
Toumi et al. (2014)	External reference pricing (ERP) modelling and experimentation project, commissioned by the European Commission. Effects include drug price erosion and spill over pricing among price referencing countries.	No	Yes	No	Discrete event simulation (DE)
Wouters and Kanavos 2013)	Evaluation of the merits and demerits of EPR from an efficiency, equity, and quality perspective. Effects include delays and inflated prices.	Yes	Yes	No	A theoretical and empirical analysis of the effectiveness of EPR
Carone et al. (2014)	ERP framework in EU. ERP have limited effects, due to difficulties in price comparison among reference countries, pharmaceutical firms tactics and can lead to inflated public drug lists.	No	Yes	No	Analytic and descriptive review
Leopold et al. (2012)	ERP in EU. Effects on drug price reduction are limited due to pharmaceutical firms pricing tactics which offset and internalize price affordability effects	No	Yes	No	Analytic review

WHO guideline on country pharmaceutical pricing policies. (2015)	ERP Policy review. Potential indirect effects of ERP, including the design and implementation of international pricing and marketing strategies by the pharmaceutical industry to counteract the effects of ERP and maximize global profits. Choice of reference countries may lead to inflated prices.	No	Yes	No	Analytic and critical review
Fontrier et al. (2019)	ERP review. ERP appears to be associated with international implications, including spillover effects, price instability, price convergence and launch delays	Yes	Yes	No	Analytic comparative review
Holtorf et al. (2019)	Survey and Literature Review to Describe Best Practices of ERP and provide recommendations. ERP can be effective only for on patent drugs and not for generic drugs.	No	Yes	No	Comparative review analysis
Maini & Pammoli 2020	External reference pricing (ERP), generates an incentive for firms to withhold products from low-income countries. ERP increases entry delays in eight low-income European countries by up to one year per drug	Yes	No	No	Structural 'moment inequality' structural equations approach
Geng & Saggi 2017	In a two-country (home and foreign) model, home's unilaterally optimal ERP policy permits the home firm to engage in a threshold level of international price discrimination above which it is (just) willing to	Yes	No	No	Game theoretic approach

	export. If the firm faces a price control abroad or bargains over price with the foreign government, an ERP policy can even yield higher home welfare than a direct price control				
Geng & Saggi 2020	In a two-country (home and foreign) model, the home producer of a branded pharmaceutical product faces generic competition in each market. Home's nationally optimal ERP policy lowers domestic price while maintaining the firm's export incentive. This ERP policy results in a negative international price spillover that the foreign country can (partly) offset via a local price control	Yes	No	No	Game theoretic approach

The above papers have used methods which apply comparative analysis, ERP reviews of practice and or statistical techniques. Such approaches can provide considerable insight for retrospective policy evaluation, but come short of strength regarding prospective policy evaluation and what if scenario analysis. This is because of the limitations of the methods they have applied. Another weakness of these traditional methods is that they do not consider causal links and time dynamics, related to main policy factors, market agents and resources, and their interconnections, and therefore cannot produce insight on and cannot answer the question why the observed (retrospectively) policy effects happen on the market.

The ERP practice in EU has been researched mainly through approaches different from simulation modelling, with the exception of one discrete event DE modelling study commissioned by the European Commission (Toumi et al. 2014), and a variation of the same model (Vogler, Lepuschütz, et al. 2015; Schneider 2017). In addition, Remuzat et al. (2015) summarised and discussed the main findings of the DE modelling study. A variation of the DE modelling was applied to evaluate the potential impact of the new AMNOG law (Integration of the discount in the list price) in Germany, on the ERP application in Europe, but published only in conference proceedings as a poster (Thivolet et al. 2014).

Tomi et al. (Toumi et al. 2014) found in their DE simulation study that ERP, considered as an isolate pricing rule led to lower drug price erosions than what could be observed in reality. They suggest that other pricing policies, potentially amplified by ERP, are involved in driving prices down, and that different scenarios illustrated spill-over and circular effects of ERP. They acknowledged that frequent price revisions, iterative price cuts, large country baskets, price calculation methods, genericisation impact and prices' sources were among the most influencing parameters on the evolution of the drug price over time. However, the explored scenarios were made in isolation to contextual pharmaceutical system complexity and did not include any account of agents' adaptive behaviour nor system resource feedback effects, according to the authors own account of their research approach and simulation method limitations. Also, the authors have not provided any verification or validation documents, which resulted in the lack of transparency and therefore cast doubts in relation to the validity of their DE results.

In that respect, important contextual (regulatory, market and competition) factors influencing drug pricing, including parallel trade, internal reference pricing, co-payment level, price linkage between the generic and original reference product, drug allocation, agent pricing tactic, competition, availability of product price information and other were not taken into account.

A key limitation was that pharmaceutical companies were not included with their decision/action routine in response to the ERP regulation (Toumi et al., 2014 ; Vogler et al., 2015), and there were no account of drug supply chain system resource and resource flow structure (Vogler and Schneider, 2015) . These are important key features and components of the pharmaceutical complex market system (Council of the European Union report, 2016) without which a proper analysis of the ERP regulation would be insufficient and incorrect (Roberts, 2015; Gilbert et al., 2018). Healthcare systems are complex systems and their analysis requires suitable methods like dynamic simulation (Marshal et al., 2015 (a) and 2015 (b)).

In the above respect, according to the "SIMULATE" checklist (Marshal at al., 2015b), the pharmaceutical market and regulation system is a complex one, having features like:

- (System) Modeling multiple events, relationships, and stakeholders;
- (Interactions) Including nonlinear or spatial relationships among stakeholders and their context that influence behaviors and make outcomes in the system difficult to anticipate;
- (Multilevel) Modeling a health care delivery problem from strategic, tactical, or operational perspectives;
- (Understanding) Modeling a complex problem to improve patient-centered care that cannot be solved analytically
- (Loops) Modeling feedback loops that change the behavior of future interactions and the consequences for the delivery system
- (Agents) Modeling multiple stakeholders with behavioral properties that interact and change the performance of the system
- (Time) Time-dependent and dynamic transitions
- (Emergence) Considering the intended and unintended consequences of health system interventions

The relevance of the above ‘’Simulate’’ check list to the ERP regulation and pharmaceutical system, and the limitations of the previous research, coming from the methods that have been applied, provide a need for further exploration of what dynamic simulation methods have been applied in pharmaceutical systems. This literature review is provided in the next section.

Table 2.1.2 Main learning points from the literature review on the ERP regulation analysis

Key insights	**Key gap from perspective of complex systems analysis requirements**
Variation in ERP apparatus can produce different effect on the pharmaceutical market system (Toumi et al., 2014; Schneider et al. 2015)	**Methodological approach:** ○ No theoretical support underpinning the exploration of the ERP effect ○ No qualitative modelling method applied ○ No system dynamic or agent based or hybrid/mixed simulation modelling ○ No treatment of the pharmaceutical system and ERP from a resource/agent interaction perspective **ERP subject exploration:** ○ No exploration of regulatory and market contextual variation interference and mediation effect on the ERP effect ○ Including other drug related regulation like INN (MOLECULE NAME) and innovative or generic brand prescribing, competitive pricing tactics and strategic behaviour of pharmaceutical companies ○ Lack of exploration for a flexible ERP regulation adequate to the local context, and from ethical and political perspective
Pharmaceutical industry responds by pricing and launch sequence strategy from higher to lower price level EU countries; and in discount based competitive tactic related to price differentiation (Vogler et al. 2015, Carone et al. 2012)	
ERP has a spill over and circular effect on product public price (Toumi et al., 2014; Carone et al. 2014, Kanavos et al. 2010)	
ERP could lead to delay, price inflation, price erosion or product deregistration (Kanavos et al. 2010, De Veerdt 2015)	
Other price regulation, market competition and parallel trade can interfere with ERP effect (Kanavos et al. 2010, Schneider et al. 2015 , Toumi et al. 2014 , Leopold et al. 2012, Richter, 2008)	
Need of ethical and political perspective to the development of flexible ERP regulation adequate to local pharmaceutical system (Persson and Jonsson, 2016, Souliotis, 2016)	
Containing expenditure through ERP could be difficult (Wouters and Kanavos 2013, Carone et al. 2014 , Espino et. al, 2011)	

2.2 Dynamic Simulation Modelling in Health care and Pharmaceutical systems

Due to the abovementioned gaps in the published papers, connected to the lack of use of methodological approaches required to explore complex adaptive systems like dynamic simulation modelling, I have further conducted research review on these methods used in healthcare and pharmaceutical systems and regulation. This is in line with the need of more comprehensive simulation modelling practice in health care. Roberts (2015) argued that "accurate representations of complex realistic systems may require hybrid approaches that use components across multiple modeling types" and remarked that "appropriate application of the dynamic methods … to the incredibly complex problems we face in healthcare today holds tremendous potential to improve the cost, quality, and efficiency of healthcare systems. Hopefully, dynamic simulation in healthcare may now come of age." Due to the gaps identified through the literature research on the ERP regulation, including limitations of the DE simulation methodology to address in a comprehensive manner the ERP regulation effects on the drug market system, I have conducted a literature review, following general methodological framework (Kitchenham 2004; McKibbon 2006), and practical application in the field (Guerrero et al. 2016a; Mahsa Keshtkaran 2015). It is suitable for searching, filtering, selecting and analysing the relevant research through on-line search engines under predefined combination of terms. For the purpose of methodological gap analysis related to the topic of my PhD research project (ERP regulation effect on pharmaceutical pricing, availability and affordability), I have conducted a search with a set of terms in relation to:

- Application of System dynamics (SD) and Agent-based (AB) modelling and simulation in healthcare
- Application of System dynamics (SD) and Agent-based (AB) modelling and simulation in pharmaceutical regulation
- Application of modelling and simulation in pharmaceutical pricing

I have focused this second literature review with the purpose to explore the use of simulation and specifically, the application of SD and ABM in healthcare and pharmaceutical markets as being the most relevant methods identified in Roberts (2015) and Marshall et al. (2015) to provide comprehensive methodological apparatus, together with DE. However, I have not included DE related search terms for two reasons: one reason is that the DE method provides limited, if no technical means to include agent decision making features (which lack in the DE treatment of the ERP was identified as a limitation), and the second reason is that using the broader term 'simulation' would provide enough means for the literature review to return results related to any kind of simulation used, including DE, mathematical, statistical or other.

The main steps of the literature review are provided on Figure 2.2.1

The goal of this literature review is to show what is the proportion of papers on application of simulation to health services in relation to the application to the pharmaceutical market and regulation. Papers have been grouped at each step and filtered, following the logic of first selecting articles with a focus on the broadest 'health' theme, then moving on to select papers that have focused on the topic of 'pharmaceuticals'. On the third step, papers were filtered on the criteria of having focused on the subtopic 'pharmaceutical regulation' and on the fourth step, papers focusing on the sub subtopic of 'pharmaceutical pricing' have been filtered and selected for further reading and analysis. All these steps were conducted through reading the abstracts of the articles, and identifying their main theme and topic.

The results of selected papers after the topic criteria of pharmaceutical pricing and regulation, are presented in Table 2.2.1, and show a huge disproportion between the SD and AB modelling and simulation application in healthcare and in pharmaceutical systems field. Only a few articles are treating ERP, however none applying either AB or SD, or mixing both approaches. Relevant papers are selected and included in Table 2.2.1 and Table 2.2.2 and Table 2.2.3 with Table 2.2.4 providing grouping and typology around each treated topic under the key theme of Pharmaceutical pricing policy and regulation.

There is abundance of modelling and simulation research studies in the health care field (Katsaliaki and Mustafee, 2011; Marshall et al., 2015; Keshtkaran et al., 2015; Li et al., 2016), however following the outcome of a bibliographical review on dynamic simulation methods applied in pharmaceutical pricing policy and regulation exploration like DE, SD and AB, there appear to be a few published papers (Table 2.2.1 in Appendix AI and full list of paper search results in Appendix AI) on a narrow topical variety. None of them presented a hybrid approach, i.e. providing any form of combination (mixing, integration) among any of the above mentioned modelling approaches in one enhanced multi-methodological framework. Application of hybrid approaches is considered important, since this can bring together a comprehensive perspective of the researched complex system (Guerrero et al. 2016a; Mahsa Keshtkaran 2015; Ackerman et al., 2014). The review excluded research on drug health technology assessment (HTA) and drug pharmacoeconomic analysis and concentrated on pharmaceutical policy and pricing regulation in EU. One paper did apply hybrid modelling and although it treated HTA topic, I have included it in the review for the hybrid SD and AB modelling framework it applied. Research gaps are found and briefly analysed and recommendation for future work is made.

The papers, which came out from the literature review are categorized and included in Table 2.2.1 (Appendix AI to Chapter 2), Table 2.2.2 and Table 2.2.3. Table 2.2.4. provides grouping and typology around each treated topic under the key theme of pharmaceutical pricing policy and regulation. A typology of the results for each treated topic and the simulation method applied can be viewed in the following Table 2.2.2 before eliminating any overlapping articles.

Table 2.2.1.

Data source	Key words: "System dynamics" AND OR "Agent-based" AND "simulation" AND "health"	Key Words: "System dynamics" AND OR "Agent-based" AND "simulation" AND "pharmaceutical"	Key words: "Pricing" AND "simulation" AND "pharmaceutical"
PuBMed	18	0	14
PMC	49	27	4
Sciencedirect	334	44	27
Google scholar	5690	832	55
Winter Simulation Conference	100	24	0
Total (non unique)	6191	927	100

Table 2.2.1 above consists of the broader contextual findings related to the number of papers under each key word combination, per electronic bibliographical source and aggregated in total number, without eliminating paper duplication and overlap among used sources.

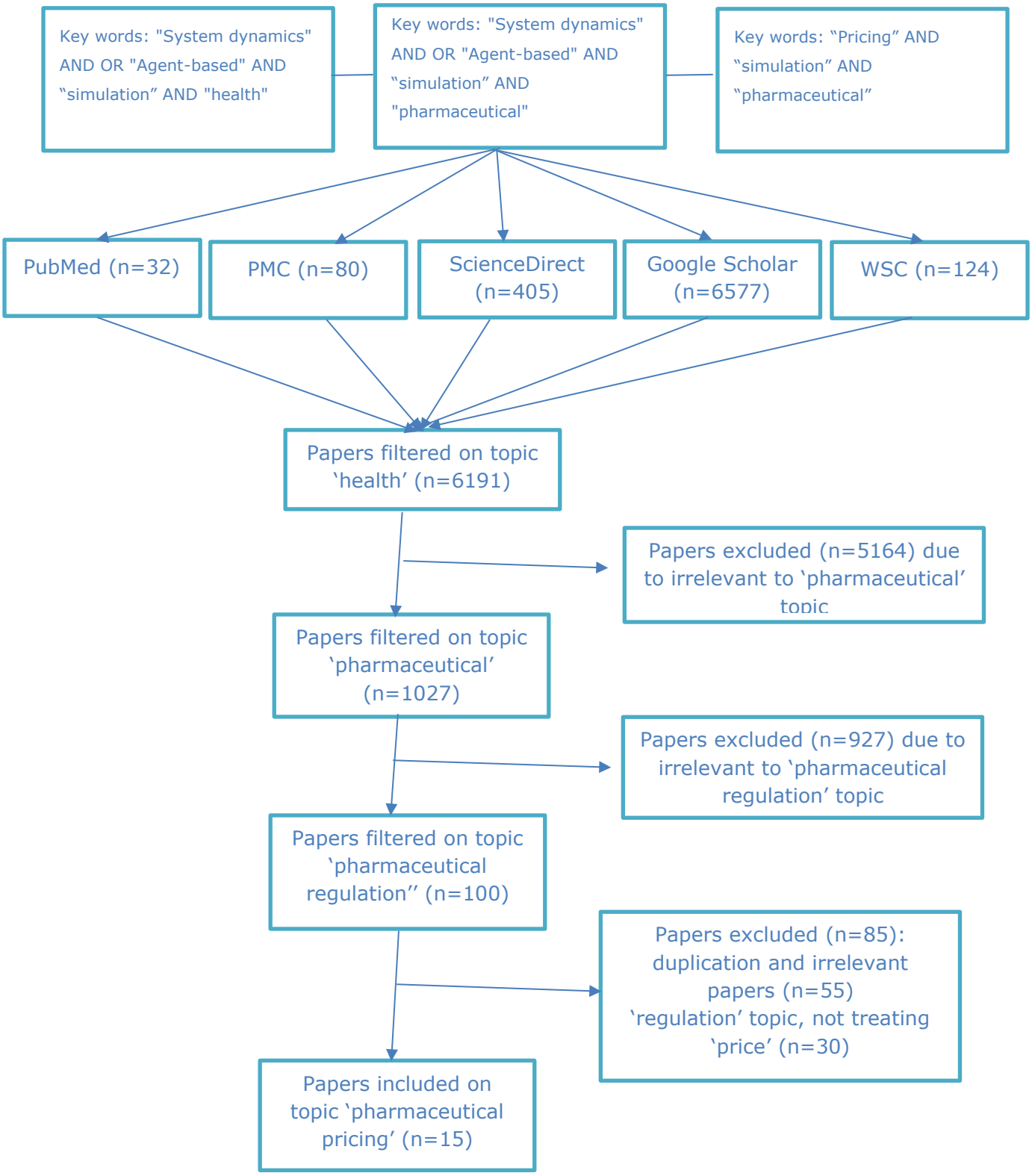


Figure 2.2.1 Flow diagram for the literature review procedure

Figure 2.2.1 above presents the procedure applied for the conducting of the literature review and with results presented on Table 2.2.2. The Figure include the search terms and their combinations that have been used and the initial search results summed below grouped after each literature (published articles) source. After this stage, papers were filtered on the criteria, first, after the topic of 'health', next, after the topic of 'pharmaceutical', third - the topic of 'pharmaceutical regulation' and fourth, the topic of 'pharmaceutical pricing'.

The total results before eliminating paper duplication show that, approximately, the published applications of system dynamics and agent-based modelling, including other simulation methods like DE, Monte Carlo and econometric in pharmaceutical systems are about 10% of healthcare application, and the number of articles treating pharmaceutical pricing are about 1.5% of the healthcare and 10% of the pharmaceutical thematic application.

The above results reveal clearly a large underexplored field, namely the pharmaceutical pricing systems one (1,5 %), on the account of health care systems which have been in the light of the modelling and simulation community for many years. The neglect of the pharmaceutical theme could be regarded to be quite surprising given that the medicinal products and their related market system combining R&D, manufacturing, supply chain and pricing are each a very important complex component of healthcare delivery systems worldwide, accounting to a great extent for their efficiency and sustainability.

An immediate recommendation coming out of the above finding would be related to an appeal toward the modelling and simulation community to direct their research attention not only to health care delivery systems but to drug delivery systems exploration too.

Table 2.2.3 Typology of each treated topic under the theme of Pharmaceutical Policy and Regulation

Topic	**Paper number**
Product co-payment / public funding	3
Pharmaceutical expenditure	2
Medicine price	4
Minimum reference price	2
Efficient utilization	2
Pharmaceutical policy mix (time to market, price co-payment, incentivizing)	1

Pharmaceutical planning	4
Inventory, availability and allocation	4
Control on access	1
External Reference Pricing	4 (1)
Impact of new drug regulation	1
Internal reference pricing	1
INN (MOLECULE NAME) competition effect on price	1
Total	30

Table 2.2.3 above exhibits a categorization by topic of a group of 30 simulation papers, after eliminating paper duplication and following a filter criterion for treating the theme of "Pharmaceutical policy and regulation", which made a starting point for further analysis and methodological exploration.

The most explored topics included in Table 2.2.3 were "Medicinal product price", "Pharmaceutical planning" and "Pharmaceutical inventory, including availability and allocation", all with 4 papers; "Price co-payment" topic follows with 3 papers; with 2 come the topics of "Pharmaceutical expenditure", "Minimum reference price" and "Pharmaceutical product utilization"; with 1 are lagging "Pharmaceutical policy mix (product time-to-market, price co-payment, controlling doctor prescribing behaviour)", "Control on product access to market", "New drug regulation impact", "Internal reference pricing", and "INN competition effect on price" .

The "External reference pricing" topic could draw additional attention due to the relative high number of papers (4) although they used only one and the same DE modelling application (Toumi et. al, 2014). That could be due to the global importance of the topic, which exploration was driven by the EC in order to facilitate the EU wide debate for medicinal product price convergence among European countries. However, the above implies that although the high international importance of the topic, only one DE modelling and simulation treatment has been made. Due to its methodological and data scope limitation (Table 2.1.1), there is a room left for future more thorough and complex experimentation through individual and hybrid qualitative and quantitative system dynamics and agent-based methodological approaches. Such approaches can provide additional conceptual and technical capabilities for overcoming the ERP DE treatment limitations.

These approaches could provide a relevant option for tackling the challenges related to the ERP which have not been treated through the published research so far, like the lack of exploration of regulatory and market competition contextual effects interfering with

ERP effects and the lack of exploration of the system from a resource and agent complex adaptive systems perspective. This is needed due to the fact that pharmaceutical market and regulatory systems are complex adaptive systems and require dynamic simulation methods like system dynamics and agent based modelling and simulation, to take account of their complex and changing interactive properties (Roberts, 2015, Marshall et al., 2015; Guerrero et al. 2016a; Keshtkaran 2015).

2.3 Dynamic simulation modelling for pharmaceutical policy and pharmaceutical pricing

The next Table 2.2.4 is related to all modelling simulation methods applied in the selected focus group of 30 papers. Narrowing down the theme from the broader "Pharmaceutical policy and regulation" to "Pharmaceutical pricing policy and regulation", lowers the number of the published research to 15 or 50% of the total number in Table 2.2.3. Clearly the "pharmaceutical pricing" topic could be regarded to be very little explored and of need of more concentrated attention for exploration in the future.

The final list of 15 papers, on the topic of pharmaceutical pricing, was reached after going through all previous stages of the literature review screening shown on the flow diagram for the literature review procedure (Figure 2.2.1).

These 15 papers are included in Table 2.2.4. However, the purpose of the literature review is to select papers that apply simulation using dynamic simulation methods as explained in Roberts et al. (2015) and Marshal et al. (2015), which further excluded papers applying other type of simulation methods different from system dynamics simulation and agent based modelling and simulation. This reduced the papers of interest down to eight and analysis of these papers are included in Table 2.3.1. One additional paper was also included, even although this paper did not focus on the topic of drug pricing (Djanatliev et al., 2015). This reason for the paper's inclusion was that the paper study applied a hybrid approach to drug policy simulation, using mixed SD, DE and AB approach.

Table 2.2.4 Selected focus group of papers applying simulation methods

Method	Paper number	Price relevant topic
SD	9	4
AB	6	2
Markov state-transition; Markov chain	2	1

Monte Carlo	1	1
State space models	1	1
Mathematical Simulation	2	1
DE	4	1
Policy simulator	1	0
structural modelling	1	1
Econometric modelling	3	3
Total	30	15

Eight papers of the group of 15 (Table 2.2.3 in Appendix AI) treating pharmaceutical pricing were filtered for further analysis due to the fact that they apply dynamic simulation modelling relevant to the call of Roberts (2015) and Marshall et al. (2015a, 2015b). One more paper is further selected to get attention too due to important methodological guidance in SD and AB hybrid simulation modelling.

Kazakov and Petrova (2015) did a study related to policy evaluation and impact assessment of alternative/what-if policy decisions connected to reimbursement policy optimization. They employed mathematical modelling and simulation of the angiotensin converter enzyme (ACE) inhibitor antihypertension drugs market with the aid of computer modelling and simulation software. The focus of their study is designing and testing a reimbursement policy based on lower patient co-payment, while at the same time providing means for controlling pharmaceutical expenditure. The simulation experiments used prescription and market data by IMS Health. These data were analysed and then used in a SD model accounting for the doctor's prescribing behavior, patient flows and public expenditure, after which they explored alternative policy scenarios by interactive learning environment or the so-called "management-flight simulator".

Main practical benefit from Kazakov & Petrova (2015) is that they have used management flight simulator SD approach to the evaluation of alternative reimbursement policy scenarios; doctors, patients and public expenditure were conceptualized as key system stocks of resources flows subject to the variability in reimbursement level as one key influencing factor regarding prescribing and compliance behaviour. Main limitation of their study was the lack of account of doctor and patient decision/action routine. Taking account of agents' behaviors would bring further insights regarding managing the system, since these agents like drug suppliers, doctors and patients are key actors within the system.

Li et al. (Li et al. 2014) examined the social problem of unreasonably high pharmaceutical costs for patients in Chinese hospitals by SD modelling. They have

addressed two problems, i.e., the unreasonably high prices of drugs and the high level of pharmaceutical fees relative to the medical costs of patients, aiming to suggest countermeasures and possible solutions. They found that if hospital and medical staff receive a higher kickback rate, they would be more likely to prescribe unnecessary expensive drugs to make greater profits, which results in unnecessary drug consumption and irrational drug use, and eventually leading to unreasonably high pharmaceutical fees. Further, they recommended that the benefit chain of the main drug suppliers needed to be cut off in order to break the link between the profits from pharmaceutical sales and the prescribing behavior of physicians, and hospital incomes. They conclude that a reformed pharmaceutical distribution system would be needed to regulate physicians and hospital interaction.

Main learning from Li et al. (2014) was that they applied SD exploration of high drug prices in hospitals and drug expenditure and explored how the drug distribution system could be improved; doctors were conceptualized as stock of resource, influenced by financial incentivizing by drug companies; They identified a feedback loop reinforcing cycle between pharmaceutical sales and hospital income and accentuated on the ethical perspective and the need for better regulation over the interaction between drug suppliers and medical staff in hospitals. Main limitation was the lack of account of agent decision/action procedure of doctors and drug suppliers.

Kunc and Kazakov (2013) developed an SD simulation of chronic cardiac disease in Bulgaria examining the dynamic behaviour of a cardiac drug molecule in the market. The objective of the study was to analyse the effect of different drug regulation policy options like providing timely access to market, influencing prescribing of generic medicines, implementing incentives for increasing the percentage of diagnosed patients. While the project developed my experience in SD modelling, it revealed limitations like experimenting with only one drug molecule, and lack of capacity to model agent interaction with key market resources.

Kazakov and Kunc (2015) developed an interactive learning environment (ILE) by the application of SD simulation model to aid the reformulation of a new generic drug launch plan. It also included an account of pricing regulation changes in the future and rival pricing competition. That helped for enhancing managerial cognition in relation to exploration of alternative product launch tactics and for finding optimal path of competitive action. The modelling experiment treated doctor behaviour, influenced by government and pharmaceutical company and patient flows, influenced by doctor allocation of drug therapy, by drug co-payment and by therapeutic compliance.

Main contribution from above was their application of a twofold doctor adoption and patient treatment stock and flow structure, influenced by pharmaceutical companies marketing, bringing in the notion for managerial resource conceptualization through the Resource-based theory (RBT) and Anticipatory systems theory lenses; In addition, authors used the modelling and simulation interactive learning environment to support behavioural experimentation with the management team. Also, they applied combination of qualitative and quantitative simulation modelling; Main limitation of their study was the lack of account of agent behaviour dependent on different decision/action routine.

Li et al. (Li et al. 2016) article introduces AB modelling by providing a narrative review of agent-based models of chronic disease and identifying the characteristics of various chronic health conditions that must be taken into account to build effective clinical- and policy-relevant models. Li et al. also identify barriers to adopting AB models to study chronic diseases and discuss future research directions of agent-based modelling applied to problems related to specific chronic health conditions. According to them, AB modelling is a promising systems science approach that can model complex interactions and processes related to chronic health conditions, such as adaptive behaviours, feedback loops, and contextual effects. However, they did not take into account in their work how agents interact and compete for limited resources.

Tang & Rosen (2014) applied AB modelling to explore what incentives could be used to overcome the widespread underuse of low cost, high benefit therapies (e.g. beta blockers and statins) and overuse of high cost, low benefit therapies (e.g. elective percutaneous coronary interventions). They use AB modelling to explore the health and economic impact of changing the financial incentives (out-of-pocket costs) faced by Medicare patients with CHD and to evaluate the incremental costs and quality-adjusted life expectancy of different policies. According to them, AB modeling, while ideally suited to model behavior change in multiple agents, such as patients and physicians, has not been well utilized in the medical decision making literature. They argue that modelling behavior change in both patients and physicians in response to targeted incentives to improve use of the most valuable therapies and reduce use of the least valuable therapies, can be of great benefit both to the effort to improve efficiency and to understand the impact of these behaviors on the system.

However, they took no account of drug companies' behaviour and doctor prescribing behaviour regarding agent competition for limited resources like budget, prescribing doctors and buying patients.

Toumi et al. (2014) applied DE in a project commissioned by the European Commission (Executive Agency for Health and Consumers (EAHC)) to further identify and assess

external reference pricing (ERP) cross-country coordination issues, such as price instability and suboptimal patient access to medicines.

The assessment was based on a DE simulation model which to identify the main parameters impacting drug price dynamics within ERP systems of fictitious and real medicinal products, with three primary objectives:

- To simulate the evolution over time of the price of any given drug;
- To simulate the impact of various changes in ERP policies;
- To support policy decision makers by identifying the drivers of the price evolution.

The model applied to the 28 EU Member States, Iceland, Norway and Switzerland was structured as a DE simulation which "allows continuous "tracking" of the pathway of an agent (here, a country) through a number of pre-defined events". Occurrence of events as well as their consequences depended on the country's characteristics (or else attributes), such as ERP rules, GDP, etc. Their model showed that ERP - considered as an isolate pricing rule - led to lower drug price erosions than what could be observed in the real life, suggesting that other pricing policies, potentially amplified by ERP, are involved in driving prices down. The different scenarios illustrated spill-over and circular effects of ERP. Frequent price revisions, iterative price cuts, large country baskets, price calculation methods, genericisation impact, and prices' sources were among the most influential parameters on the evolution of the drug price over time through ERP-based systems. The simulations support previous studies on industry's incentives to engage into launch sequence strategy. However, the simulation model did not show any substantial price convergence over time and it remains unclear whether price divergence would be larger without ERP (Toumi et al., 2014).

The DE model capability to account for the complexity, non-linearity, feedback, and adaptability of agent-like and resource system-like features of the pharmaceutical market could be admitted to be highly limited. First, the methodological technique applied is limited to tracking queue-like country-agent behaviour, related to comparing and reacting to change in drug prices, through predefined launch events. Next the ERP modelling experimentation, due to the narrow modelling boundary, treated ERP to be the only price setting tool. Third, it did not account for company proactive and reactive behaviour to actual or expected ERP market effect, neither for generic drug competition (Toumi et al., 2014; Vogler et al., 2015).

In order to produce a simulation model which represents a flexible and efficient tool for decision makers, the methodological technique applied needs to allow for realistic modelling of the above mentioned pharmaceutical market system characteristics. In

addition, important contextual (regulatory, market and competition) factors influencing drug pricing, including parallel trade, internal reference pricing, co-payment level, price linkage between the generic and original reference product, drug allocation by innovative or generic brand or by INN (MOLECULE NAME), rival pricing tactic, availability of product price information and other were not taken into account, making the model far from being reliable and capable to aid pricing policy. Furthermore, the DE model and related publication while exhibiting an advancement in the modelling exploration of EU pricing policy like ERP, did not provide access to detailed information about model input variables, model equations, structure and coding, which prohibit independent data audit, model validation and verification of the results and therefore casts doubt on the credibility of ERP policy implications that arise from their work.

This 'lack of transparency' means that the DE simulation results cannot be taken as a reliable source for policy recommendation. This issue is also in addition to the model's methodological limitations which include: the lack of account of market agents behaviors and the dynamics of supply and demand resource flows with respect to the ERP regulation, in addition to the lack of consideration of local contextual regulatory and competition factors that interfere with the main regulation effects.

In this respect, the DE simulation outcomes do not include analysis of questions regarding drugs access and availability (entry delays or market exits). Questions regarding drugs affordability are analysed by treating ERP as an "isolated pricing rule" (Toumi et al., 2014) mechanism, without taking account of interfering market and regulatory factors (supply and demand actors, supply chain and resource dynamics, market competition tactics, on patent and off patent medicines, parallel trade, drugs prescribing, etc.)

For all the reasons outlined above, policy recommendations arising from the DE simulation results might support incorrect decision making by misleading drug price authorities at local or EU level to follow ERP policies, which might produce unintended consequences such as facilitating excessive drug pricing or drugs delays and unavailability.

All of the above limitations and lack of transparency of the DE simulation treatment of the ERP, produce doubts for its conceptual and technical capabilities to support pharmaceutical policy decision makers. In this regard, the results could provide misleading evidence and could support ineffective recommendations for policy changes. For this reasons, further simulation research is required which accounts for all the outlined gaps and limitations.

Table 2.3.1 presents a categorization of the eight papers that were selected and used in the discussion in the previous paragraphs, according four criteria: topic (within the main theme of pharmaceutical policy and regulation), methodological framework (SD, AB, DE or combination between them), theoretical framework (in support of their approach) and limitations. The table provide evidence that only one paper from all eight, used a hybrid methodological approach. Also, two papers mentioned the use of a theoretical framework in support of their applied methods. All papers, except one (which used a hybrid methodological framework), acknowledged limitations connected with methods that they have applied. Most of these limitations came from the limited perspective that a single method could provide, thus neglecting perspectives that other not used methods could have provided. These were related to either not considering agents' behaviours and rules within the system, or resource components and their interconnection within the simulated systems, or not taking into account a wider comprehensive system perspective.

Table 2.3.1 Categorization of the selected papers from the literature review on the criteria of main topic, methodological framework, theoretical framework and limitations

Publication	Topic within the Pharmaceutical Pricing Policy and Regulation theme	SD, AB, DE, Hybrid	Theoretical framework	Limitations
Kazakov and Petrova (2015)	Evaluation and impact assessment of what-if policy decisions related to level of product price co-payment and reimbursement of ACE inhibitor on health outcome and public pharmaceutical expenditure	SD	Not mentioning theoretical framework	Not taking in account the decision making rules of market agents
Kazakov and Kunc, 2015	Market competition structure and product launch pricing	SD	Resource-based View (Barney 1991; Wernerfeldt 1984; Peteraf 1993); Behavioural theory of the firm (Cyert and March 1963), Anticipatory systems theory (Rosen 1985)	'Not linking the results with the long-term performance of the firm' Limited to evaluating managerial cognition before and after working with a scenario simulator Not considering market agents decision behaviour
Li et al., (2014)	Analyzing unreasonably high prices of drugs and the high level of	SD	Not mentioning	Not considering 'specific hospitals, individual patient

	pharmaceutical fees relative to the medical costs of patients		theoretical framework	characteristics, and social insurance schemes. The governmental supervision system and adaptive changes of manufacturers, distributors, hospitals, and physicians are not taken into account in the intervention trial measures'
Kunc and Kazakov (2013)	Predictive evaluation of pharmaceutical policy component mix (time to market of new generic medicine, product co-payment level, incentivizing generic prescription) and pharmaceutical public expenditure (pricing)	SD	Not mentioning theoretical framework	Not considering research on doctors and patients' behaviour in connection to the design of healthcare policies'
Li et al. (2016)	Chronic health clinical and policy relevant analytical review and recommendation for future work in CVD to include modelling the effect of drug therapy	AB	Social norms theory (Cialdini and Trost, 1998)	Not taking into account the 'effects of different treatment strategies, drug therapies, and procedures'; No perspective of the whole system and systems resources
Tang et al. (2014)	Coronary heart disease (CHD): underuse of low cost, high benefit therapies (e.g. beta blockers and statins) and overuse of high cost, low benefit therapies (e.g. elective percutaneous coronary interventions); Health and economic effect of changing financial incentivizing (out-of-pocket expenditure)	AB	Not mentioning theoretical framework	Limited to the 'exploration of the health and economic impact of changing the financial incentives (out-of-pocket costs) faced by Medicare patients with CHD', connected to choosing a cost effective treatment; Lacking account of other components in the whole healthcare system, including resources
Toumi et al. (2014)	External reference pricing policy (regulation) evaluation (isolated effect of ERP on drug prices in ERP countries)	DE	No mentioning theoretical framework	'Parallel trade was not modelled in this project, … the potential economic impact of parallel trade was not assessed'

				'ERP - considered as an isolate pricing rule - led to lower drug price erosions than what could be observed in the real-life, suggesting that other pricing policies, potentially amplified by ERP, are involved in driving prices down'; Drug price scenarios are compared using average drug price evolution among all ERP countries, which does not have statistical significance nor exhibit drug price evolution per each country
Djanatliev et al. 2014; Kolominsky-Rabas et al., 2015	Hybrid: Application of hybrid SD/AB simulation modelling for Prospective HTA for mobile stroke units	Hybrid (SD, AB and DE)	No theoretical framework mentioned	No limitation in connection to the technical capabilities of the methodological approach; Limited account for the agent's behavioural decision rules in connection to agent resources interaction;

This section explored the application of dynamic simulation modelling methods in pharmaceutical market and regulation. It showed main insights and limitations of using only one individual method in comparison to the perceived benefits of combining individual methods in hybrid applications, for the purpose of gaining a comprehensive view of the researched complex system.

2.4 Research on combining system dynamics with agent-based modelling and simulation in a hybrid multi methodological framework

This section presents a review on system dynamics and agent-based simulation and on the research relevant to the scientific discussion on the practical mixing of the system

dynamic and agent-based modelling methods, and on the associated benefits regarding the exploration of complex systems. Comparison of the two methods is provided and key limitations are outlined in the perspective of the possibility of overcoming them by the appropriate complementary combination between different features in both approaches. In that regard, a classification of alternative paths to bringing them together is also provided in the light of Roberts (2015) call for the application of hybrid modelling and simulation in health care.

2.4.1 System Dynamics Modelling (SD)

2.4.1.1 Theory and practice

Forrester (1958) pioneered SD practice following two key concepts of systems theory related to the feedback loops principle, and to the principle that system's structure drives system's behavior. A main view behind the behavior of complex dynamic systems identifies hidden endogeneity and feedback effects due to delay in time and bound rationality, leading to non-linear and often counterintuitive behaviour (Sterman, 2000; Morecroft, 2007). Hence, systems dynamics modelling practice tries to uncover the hidden mechanisms underlying the observed non-linear effects in the economic systems "instead of only treating their symptoms" (Forrester, 1958).

Main building blocks in SD modelling are stocks or resources (Richardson & Pugh 1981; Forrester et al. 1976; Wolstenholme 1999; J D Sterman 2000b), flows and auxiliary variables which can involve a quite large number of differential/integration and algebraic equations in only one model, depending on model boundary and complexity.

Understanding the endogenous and exogenous characteristics of organizational and market complexity, being a source of causal ambiguity, emergent behaviour and self-organizational dynamics (Morel and Ramanujan, 1999) is well advanced by general systems theory (Von Bertalanffy 1968; Andrew 2003) and the system dynamics field of research (Forrester, 1961; Forrester 1995; Radzicki & Sterman 1994; Richardson & Pugh 1981; J Randers 1980; Morecroft 1999; Sterman, 2000; Morecroft, 2007). Systems complexity comes from dynamic components and their nonlinear interactions which cause emergent behaviour, the reasons for which are hardly obvious. The more complex interrelations are among the systems internal and external components, the more ambiguous are the causes of the system behaviour and its self-organizational dynamics.

System dynamics research has tackled important questions related to strategy, organizational behaviour, policy and operations and purposive managerial decision making as a primary source of market dynamics and performance heterogeneity. Research also has shown that system dynamics modelling and simulation is able to account for the real world information feedbacks, delays, nonlinearities caused by organization and market complexity and can explain organizational and market behaviour. Healthcare and pharmaceutical systems are dynamical complex systems and exhibit nonlinear behaviour which can be better explained by dynamic modelling approaches like system dynamics rather than traditional linear modelling (Roberts 2015; Marshall, Burgos-liz, et al. 2015) In that regard, system dynamics approach can be appropriate to explore the ERP regulation effect on the pharmaceutical market system behaviour, which is explained in more detail in chapters 7 and 8 of my PhD thesis.

2.4.1.2 How to do SD

System dynamics methodological framework follows a complex non-linear and feedback view of the world with accumulation and depletion of resources and time delays. In order to model complex non-linear systems, modellers apply qualitative modelling technique capable to capture their complexity in order to support quantitative model building or use them on their own, like influence and causal loop diagrams (Randers 1976; Morecroft 1982; Wolstenholme 1982; Coyle 2000), cognitive mapping (Eden 1988; Eden & Ackermann 2000; Ackermann et al. 1992; Ackermann & Eden 2010; Huff 1990; Eden 2004; Ackermann 2012); for example, combining qualitative with quantitative modelling approaches (Howick & Ackermann 2011) like the modelling cascade (Howick et al. 2008) shows how they can support each other and enhance confidence among modellers and users. CLD are standard approach to SD model conceptualization regarded as qualitative modelling used on their own and to support the building of a quantitative SD simulation model. An example of mixed modelling approach like the modelling cascade (Howick et al. 2008) consisting of a cognitive and causal mapping framework of influence maps, formal system dynamics influence diagrams/causal loop diagrams is a specific application of mixed modelling designed with the aim to facilitate group model building and gather multiple perspectives in practice, i.e. to support the elicitation of the managers' mental model when working with clients and build confidence in the modelling process and output.

The qualitative tools and quantitative tools applied in the system dynamics modelling, like causal mapping and numerical simulation have the purpose to help the modeler to capture feedback loop processes endogenous to the system, how they are dependent on the stock and flow structure of the system, and how they produce emerging complexity and system's behaviour (Sterman, 2001).

Conceptualizing and building a system dynamics model involve four key stages: CLD, Stock and flow diagram, Equation coding, and Simulation. The modelling process need to be iterative following five general steps (Sterman, 2000): problem articulation (boundary selection), dynamic hypothesis, simulation model formulation, model testing and policy evaluation. Following Randers (1980) guide to model conceptualization, modelers need to follow a conceptualization, formulation, testing and implementation stage. Richardson & Pugh (1981) and Roberts (1981) view the model building stages as problem definition, system conceptualization, model formulation/representation, model behaviour and analysis, evaluation and policy analysis and use.

All the above three perspectives provide a similar if not the same, logical sequence of steps for conceptualising, building, validating and use of SD simulation models, but utilising different terms for each stage.

Following Randers (1980) classification, the first "conceptualization" stage needs to account for the modeler conceptual understanding of the system components and how they are influencing each other's behaviour. To this aim come the qualitative techniques like influence/causal loop diagrams which help the modeler also to explore model boundary and generate dynamic hypothesis for simulation testing. The next "formulation" stage is linked to the quantitative model building, meaning that normally a stock and flow formal diagram need to account for the system structure and for the proper mathematical interrelations among the model variables, including coding in the model. The next" testing" stage is about model calibration and verification having the purpose to prove the proper quantification of the simulation model. The "implementation" stage is associated with the simulation application to policy evaluation by doing what if scenario simulations in order to test previously identified hypotheses and find how variation in key input variables influences the behaviour of the whole system.

A typology of common behaviour emerging within dynamic systems and exhibited by system dynamic simulations can be related to exponential growth, goal seeking, and oscillation (Sterman 2000; Morecroft 2015; Howick & Whalley 2007; Ghaffarzadegan et al. 2011; Kunc & Andrade 2010; Luke & Stamatakis 2012). Any of that behaviour is generated by a simple feedback structure, for example, related to positive/reinforcing feedback in respect to exponential growth, or negative/balancing feedback in respect to

goal seeking, or a combination of negative feedback with time delays in respect to oscillation. Nonlinear interactions between feedback structures can further produce S-shaped growth, S-shaped growth with overshoot and oscillation, and overshoot and collapse Sterman (2000). Feedback loops are identified to be inherent endogenous circular interrelations among system variables responsible for the above described nonlinear behaviour. The scientific concept of feedback loops can be associated with system control theory or cybernetics (Umpleby & Dent 1999; Von Foerster 1979; Von Bertalanffy 1972) , to become a key endogenous mechanism in system dynamic approach and system dynamic modelling and simulation (Forrester 1961; Morecroft 1982; Wolstenholme 1999; Wolstenholme 2004; Barlas 2002; J Randers 1980) . Feedback is considered to be a key principle in understanding system behavior and in doing qualitative and quantitative modelling by SD methodological apparatus .

2.4.1.3 Verification and Validation

Sterman (2000) highlights that since a model is a simplified representation of reality it can never be validated and building confidence in a model is more appropriate. Critically assessing model's boundary, time horizon, and level of aggregation in relation to modelling purpose is of key importance and all factors relevant to the modelling purpose need to be captured endogenously in the model boundary.

When making validation tests, modelers need to account for Boundary adequacy, structure assessment, dimensional consistency, model behaviour reproducibility, integration validity, behaviour inadequacy, behaviour surprise, sensitivity analysis and confidence building by summary statistics (Barlas 1994; Barlas 1996; Barlas 1989; Barlas & Kanar 2000; Barlas & Carpenter 1990) and Coyle & Exelby (2000), Coyle (2000) have introduced model behaviour pattern evaluation through appropriate pattern oriented measures. Morecroft (2007) gave a practice example for the application of model validation and confidence building by performing tests of model behaviour, including visual and statistical fit; of model structure, including boundary adequacy, dimensional consistency, and relevance to existing knowledge, extreme conditions, and parameter verification; and tests of learning to explain simulation results and policy implications.

Mingers (2000) explained model validation from a critical realism (CR) point of view: "… the philosophy is similar to that of CR (as opposed to positivism) in that it is recognized that the main purpose is not accurate prediction of what will occur, but instead greater learning and under-standing of the causal mechanisms involved in the situation. The

argument is the same as in CR, namely that social systems are inherently open (although they have to be artificially closed within the modelling process) and that it is impossible to properly quantify the various factors and their relationships. This fits well with Bhaskar's Diagnosis, Explanation, Action methodology for bringing about change." (p. 1265) According to him, "If the model can replicate the observed (or desired) behaviour this is good, although not definite, evidence that the model captures the actual causal mechanism at work. It is also recognised within SD that the model cannot be proved to correspond to reality, and that in the validation stage of model building the process will at least partly involve attempts to eliminate or disprove alternative possibilities." (p. 1264).

2.4.2 Agent Based Modelling and Simulation (ABM)

2.4.2.1 Theory behind ABM

According to Axtell (2001) agent-based modelling compared to traditional approaches to modelling economic systems could be a more viable approach when there are reasons to think in terms of agents. For example, when the problem/RQ we need to explore is naturally represented by a large number of agents which decisions and behaviors which can be well-defined, exhibit adaptation and change, learning and engaging in dynamic strategic interactions, and relationships with other agents, can have a spatial component to their behaviors and interactions. A very important feature of Axtell's AB modelling criteria is linked to the structure of the system which has endogenously emerging mechanisms governing its future evolution and is not dependent only on the past (Axtell, 2000).

Macal and North (2010) acknowledge that ABMS could be linked to complex systems (Weisbuch, 1991) and complex adaptive systems (Kauffman, 1993; Holland, 1995) theory and exploration. They understand ABM as a set of "ideas, techniques, and tools for implementing computational models of complex adaptive systems" with the aim to reveal origin of self-organization, emergent phenomenon, and adaptation (Macal and North, 2010).

2.4.2.2 Agent-based Models

The behavioural rules, emergence and adaptation effect of agent behaviour are tightly connected with the theory of complex adaptive systems (CAS) which do not have a controlling centre and a fixed structure, rather they are structurally coupled with their environment and exhibit a co-evolutionary emerging feature, i.e. as the result of decentralized bottom-up decisions and behaviour of individual entities or agents over time (Guerrero et al., 2016; Macal, 2010; Macal and North, 2006). Agents' decisions and behaviour "shape and change the state and structure of the system and react to the dynamic changes in the system, which can potentially alter their decision rules" (Guerrero et al. 2016).

Agents have decision rules and autonomous actions, and interact with their environment forming non-linear and feedback effect. (Epstein and Axtell, 1996; Bonabeau, 2002; Phelan, 1999; Phelan 2001). Agents' decision rules which govern agents' behavior are linked to a goal-oriented behavior related to achieving a certain individual benefit, guided by the behavioural principle of satisficing /criteria of accessibility, risk aversion, and anchoring and adjustment/ rather than maximizing a utility function (Kahneman, 1979) due to their bound rationality and incomplete knowledge (Simon, 1959; Jennings et al., 1998) and unequal distribution of information (Akerlof, 1976; Stiglitz, 2000). Interestingly, according to Phelan (1999) when agents coordinate their decisions to achieve common goals, a "collective intelligence" phenomenon may emerge According to Schieritz, N. (2002) the building blocks of AB modelling are the individual agent, agent behavioral rule, inner and intra agent feedback connection, adaption of agent behaviour, inductive inference from individual agents' behavior to system behavior and discrete or continuous time frame. The agent pattern of behaviour or schema is "a cognitive structure that determines what action the agent takes at time t, given its perception of the environment" (Anderson, 1999) and can change or evolve in order to adapt to the agent environment.

2.4.2.3 How to do ABM

Macal and North (2010, 2007, 2014) give the relevant structure of an agent-based model, which a modeler needs to account for when identifying, modelling and programming to create an ABM: "1. A set of agents, their attributes and behaviours; 2. A set of agent relationships and methods of interaction: An underlying topology of

connectedness defines how and with whom agents interact; 3. The agents' environment: Agents interact with their environment in addition to other agents."

From a practical modelling standpoint, they consider agents to have the following essential characteristics:

- An agent is a self-contained, modular, and uniquely identifiable. Agents have attributes that allow the agents to be distinguished from and recognized by other agents;
- An agent is autonomous and self-directed. An agent can function independently in its environment and in its interactions with other agents;
- An agent has behaviours that relate information sensed by the agent to its decisions and actions. An agent's information comes through interactions with other agents and with the environment. An agent's behaviour can be specified by anything from simple rules to abstract models relating agent inputs to outputs through adaptive mechanisms;
- An agent has a state that varies over time. Just as a system has a state consisting of the collection of its state variables, an agent also has a state that represents the essential variables associated with its current situation;
- An agent is social having dynamic interactions with other agents that influence its behaviour;
- An agent may be adaptive, for example, by having rules or more abstract mechanisms that modify its behaviours. An agent may have the ability to learn and adapt its behaviours based on its accumulated experiences;
- An agent may be goal-directed, having goals to achieve (not necessarily objectives to maximize) with respect to its behaviours. This allows an agent to compare the outcome of its behaviours relative to its goals and adjust its responses and behaviours in future interactions;
- Agents may be heterogeneous. Agents may also be endowed with different amounts of resources or accumulate different levels of resources as a result of agent interactions, further differentiating agents.

In relation to the simulation modelling exploration of the ERP effect on the pharmaceutical resource/agent system, the above list of agent features will refer to the adaptive behaviour of pharmaceutical companies in response to the ERP regulation, and

the behaviour of other agents included in the simulation model. More will be explained in the relevant chapters on qualitative and quantitative modelling.

According to Macal and North (2010), "a theory of agent behaviour for the situations or contexts the agent encounters in the model is needed to model agent behaviour. A modeller may apply a behavioural model if there is available empirical data to support the application, relevant to behavioural framework and empirically based heuristics (Sun, 2006). In that regard behavioural decision theory (Kahneman & Tversky 1979) and anticipatory systems theory (Rosen 1978; Butz & Pezzulo 2008) can greatly enhance ABM application (explained in Chapter 8 and Chapter 9).

2.4.2.4 Verification and validation of ABM

Verification and validation of ABM need to be connected to the theoretical, conceptual and operational criteria for agent-based modelling and simulation. Heath et al. (2009) provide useful generalization regarding ABM validation, with two main stages: conceptual and operational validation, where the built conceptual model needs to correspond to the applied system theory and behavioural criteria and the obtained results from the simulation runs need to be consistent to real system behaviour.

Bonabeau (2002) accentuated that validation and calibration needed expert judgement, while Ormerod and Roswell (2009) talk about model replication, model explanation, and outcome explanation and that "behavioural rules should be capable of justification using evidence from outside the model". Another ABM validation methodological framework developed by Klugl (2009) included the following stages: conceptual and implementation verification of a runnable model through face validation, sensitivity analysis of a plausible model, model calibration and statistical verification.

In relation to the ERP focus of my PhD research, the validation framework needs to build confidence in pharmaceutical system stakeholders that the AB modelling and simulation approach is theoretically sound and can provide conceptually and operationally true representation of market agents cognitive and behavioural model in regard to agent decision making and action routine.

2.5. Integrating system dynamics and agent-based modelling

Although main terms in theories supporting SD and AB modelling coincide like system, emergence, dynamic, nonlinear, adaptive and hierarchy etc., the practical apparatus of the first is focused mainly on "confirmatory analysis" from the perspective of problem solving and generating consensus for system improvement, the practice of the second is focused mainly on exploratory research of the emerging properties of the system (Phelan 1999).

Further comparing the above two modelling frameworks, a key limitation of the SD approach, is that stocks and flows are related to the quantity rather than to the quality and that SD models have fixed structure and lack of capability to modify structurally and to adapt their levels, rates, and equations in response to environmental change (Phelan 1999); (Schieritz 2002; Schieritz & Milling 2003), which is one of the distinctive capacities of agent-based models, which by their nature consist of a set of autonomous or semiautonomous agents (Parunak et al. 1998; Macal 2010; Axtell et al. 2001; Bonabeau 2002). Following the above, Schieritz (2002) advocated for an approach of integrating system dynamics and agent-based modelling comparing the two modelling frameworks and finding room for complementarity and enrichment between both (Table 2.5.1).

Principle	**System Dynamics**	**Agent-Based Modeling**
Building block:	Feedback loop connecting behavioral variables	Individual agents connected by feedback loop
Object of interest:	Structure of the system	Agents' rules
Research approach:	Deductive: infer from structure to behavior	Inductive: infer from individual agents' behavior to system behavior
Development of object of interest over time:	Structure is fixed	Agents' rules can be adaptive
Handling of time:	Continuous simulation	Discrete or continuous simulation

Table 2.5.1 Comparing the two frameworks

Schieritz and Milling (2003) brought further in the debate of integrating SD and AB the metaphor of "modeling the forest or modeling the trees" where they argue that an

integrating approach would need to take concern about modelling the whole picture, and not concentrate on micro only or macro only level. A call for joint research between agent-based and system dynamics modeling by Scholl (2001) proved to have quite an effect among the modelling community recently accounted by (Guerrero et al. 2016). Scholl (2001) made a point that "Rather than benefiting from one another, the two disciplines (agent-based and System Dynamics modeling) ignored each other's literature almost entirely", while being major non-linear modeling techniques, and argued that "AB and SD joint research may have the capacity for delivering results superior to those based on one technique only."

Holland & Miller (1991) viewed scientific models as either linguistic or mathematical, and pointed out the high level of flexibility of the first and the rigor in formulation and structure of the latter, which could be taken as relative strengths and weaknesses, naturally supporting more constructivist or positivist research frameworks, depending on the researcher's "ontological and epistemological vantage point" (Scholl 2001).

Agent-based modeling focuses on agents interacting by following rules and rule routines, discovered by observation or by reverse direction of study, following an inductive approach, while dynamic systems are deductive having feedback structure which differentiates the level of system analysis in both approaches into looking for leverage points in rules and agents in the former, and in the feedback structure in the latter (Scholl 2001).

Stock and flow structure in SD paradoxically could not be dynamic but remain static; it could not change and could not be capable of emerging behaviour and flexibility like the ABM (Hans J Scholl 2001; Schieritz 2002; Guerrero et al. 2016a; Schieritz & Milling 2003); ABM could contribute, having that capability, by integrating the agent rule following behaviour into the SD modelled environment. However, one way to bring in "quality" and flexibility within the SD models structurally can be achieved by „letting" agents interact with stocks and flows, i.e., by integrating each modelling paradigm with one another. This can allow the agent decision/action routine and agent attributes to interact with inflow and outflow rates of stock accumulation and depletion, and can transfer agents' adaptive capability to support structure changes by reordering, inclusion of new and/or elimination of predefined stocks and flows to account for emerging structural flexibility (Guerrero et al. 2016a; Schieritz 2002; Schieritz & Grossler 2003).

A paper on the theme on integrating SD and AB modelling and simulation, authored by Guerrero et al. (2016) interrogates about the potential benefits of integrating both methods and about what theory can unite and support that integration. They agreed with Macal (2010) and Scholl (2001) that differential features between both in scope, focus on

system or on emergent behavior, aggregation level and the AB capacity to explore heterogeneity and spatial variability, make each paradigm more suited to different situations. The authors posit that, although SD and AB differ in capacity to model continuous aggregated and discrete disaggregated system states, physical space, topographies, and network structures; stochastic & deterministic phenomena, learning and adaption, combining or integrating both can prove beneficial by modelling "some components discretely and in a disaggregated fashion, while other components can be modelled continuously and in an aggregated fashion, based on the different system characteristics and the specific model purpose'' (Guerrero et al. 2016). For example, in complex adaptive systems, where resource flows behaviours are simulated continuously and agents activities follow a discrete pattern, their interactions will require a hybrid SD - AB framework in order to grasp the internal dynamics of the modelled system.

In this way, a hybrid SD/AB model facilitates the definition of appropriate levels of aggregation for each component of the system and can be particularly relevant when the modelled environment contain configurations of agents and resources interactions (Popkov & Garifullin 2007; Borshchev & Filippov 2004; Kolominsky-Rabas et al. 2015) Furthermore, for many modelling problems, a combination of SD and AB can reduce computation times, provide the strategic overview characteristic of SD, while still capturing relevant elements of the individual heterogeneity and stochasticity of entities and processes (Guerrero et al. 2016a) Depending on the modelled environment resource or agent like features, one or the other modelling and simulation approach could be regarded as being more appropriate. However, in resource/agent symbiotic environment, natural hybridization of the modelling approach could be argued to bring further benefit for the complementarity in the macro and micro treatment of the system elements (Hans J Scholl 2001; Schieritz 2002).

Another potential advantage of combining SD and AB is that this can be seen as a way to enhance the capability of SD models to cope with spatially explicit problems like movement of agents and/or resources in the geographical environment from one place to another (Popkov & Garifullin 2007; Borschev 2008; Borshchev & Filippov 2004; Borshchev 2007; Viana 2015; Djanatliev & German, 2015), i.e. mobile technology response to cardiovascular patients, drug manufacturers supplying different local markets in EU, drug distribution network, and other. The resulting models permit arranging agents in a spatial or network structure, while integrating important properties of SD, such as continuity and non-linear multi-loop feedback. This approach can be refined when the individuals are mobile and consequently the spatial dimension becomes dynamic, like in supply chain and distribution networks. Besides this, it is possible to use multiple SD sub-models to create different properties across a spatial grid. As a result,

individuals interact with different SD sub-models depending on their position (Vincenot et al., 2011). Agents can plausibly even interact with more than one SD sub-model at a time when their decision/action routine need to influence the stock and flow dynamics in parallel in different sub system structures.

Looking for a typology of mixing both methodologies, different generalization can be found one of which made by Swinerd and McNaught (2012) after Shanthikumar and Sargent (1983), which differentiated three classes depending how SD or AB models interact: "1/ A sequential class, in which the outcome of each module forms the input for the next module 2/An interfaced class, which includes non-sequential combinations of modules that do not influence each other but combine their independent outcomes to produce the model outcome; and 3/ An integrated class, in which modules and even model outcomes provide feedback to one another".

Another typology made by Vincenot et al. (2011) identified four typical SD-AB structures: "1/ AB agents interacting within their SD module – environment, where emergent properties from the AB module can dynamically parameterize the SD module; 2/ AB agents containing SD modules that determine their dynamic decision rules and spatial structures, and 3/ individuals interact with an environment made of more than one SD module, depending on the agent's position and the SD module's area of influence; 4/ SD-ABM model swapping."

Different classifications for mixing SD/AB modelling and simulation, like the above, are developed to account for the way both methodological approaches interact (Swinard and McNaught, 2012) or are structured (Vincenot et al. 2011), whether in a sequential, independent or in an integrated mode. More flexible would be to regard the combination of both modelling paradigms as hybrid which is a broader term not restricting combinations to a narrower scope, due to the fact that model elements can communicate between, depending on the level and degree of combination among the multi-paradigm model architectures, being they on macro, micro or middle dimension (Borshchev and Filippov, 2004).

Morgan et al. (2017) provide a review of different ways how SD and DE methods can be mixed, and generalised a framework of five designs for using simulation methods together: "parallel design", "sequential design", "enrichment design", "interaction design" and "integration design". This framework can be used also for supporting the joint use of SD and AB methods. Another classification can be linked to the representation of modelling process being continuous, like in SD, or discrete, like in AB, and that mixing different approaches means hybrid integration of continuous and discrete event behaviors systems according to Popkov and Garifullin (2007).

Le Khan et al. (2021) provided a recent review on the SD and AB combination approaches. Their generalization include the following types of hybrid designs: parallel, sequential, interaction, integration and enrichment. According to the authors, the first type occurs when both modules do not interact, the second one – when modules interact only once, the third one – when modules interact multiple times and operate independently, the fourth one – when modules interact multiple times but cannot operate independently, and the fifth one – when one module dominates over another.

No matter of what classification is followed, the goal of SD and AB combination seems to be related to the creation of more "accurate" (Ghaffarzadegan et. al, 2011) hybrid models (Djanatliev & German 2016; Lättilä et al. 2010; Roberts 2011) in respect to capturing different levels of systemic granularity from quality (agent decisions), and quantity (resource flows) perspective. "Accurate" here means that hybrid method combinations have the capabilities to capture better the behaviour of the simulated systems and their components due to their enhanced technical apparatus. Ghaffarzadegan et al., also talk about 'accurate representation' of simulated real systems, regarding comparing simulated vs real 'pattern' of behaviour of those systems (Ghaffarzadegan et al. 2011, p.p. 29 and 30).

2.5.2 Hybrid modelling and simulation application in pharmaceutical policy and regulation

A lack of broad hybrid system dynamics and agent-based modelling practice in pharmaceutical market systems, policy and regulation, and a growing need for application of dynamic simulation methods, publicly announced by Roberts (2015) have been charting the boundary of a widely underexplored territory. One of the few hybrid system dynamics and agent-based models recently provided in Djanatliev et al. (2012; 2014) was focused on Prospective Health Technology Assessment (ProHTA) approach with the aim to explore the effects of new innovations early before the "expensive and risky development phase begins." They have considered two key questions related to "economic prognoses and/or impacts on patient's health" like: "How can a new technology be optimized prospectively after the observation of simulated effects?" and "What innovation is required to reach desired output values?". Similarly, my PhD project can further contribute to prospective policy evaluation questions. For example, how a price regulation policy can be optimized prospectively by simulation. And what specific interventions are needed in order to a achieve a policy goal of equitable access, availability and affordability of drugs in the EU local markets.

In their model they identified four modules as important ones which have conceptual relevance to my ERP modelling project: Population Dynamics; Disease Dynamics; Health Care Delivery; Health Care Financing. Djanatliev et al. (2013) experimented with extending their proHTA model to combine system dynamics, discrete-event and agent-based simulation by adding a middle layer due to the need to model the workflow of a mobile unit, providing an intermediate link from the micro agent level to the macro environment modelled by system dynamics. The above hybrid methodological conceptualization could be extended and analogically applied to pharmaceutical pricing policy and regulation having in mind the critical role of the pharmaceutical products for the health outcome of a medical treatment. To that goal, pharmaceutical product flow and pricing dynamics need to be naturally connected to drug supply and demand factors along the pharmaceutical distribution chain.

In relation to the need of developing further a hybrid /multi-methodological paradigm/ modelling framework, Lynch et al. (2014) proposed a multi-paradigm modeling framework (MPMF) for modeling and simulating problem situations. The benefit of the framework relates to identifying "different levels of granularity (macro, meso, and micro)" which are linked to the relevant modelling paradigms in order to combine them for a more comprehensive modelling of the problem situation", which correlate to the hybrid modelling community practical and theoretical implications (Roberts 2015; Marshall, Burgos-liz, et al. 2015; Djanatliev et al. 2012, 2013, 2014; Borschev and Filipov 2004; Popkov and Garifulin 2007). Complex system behaviour can be grasped and reproduced better by a holistic and comprehensive (Rosenhead 2006; Ackermann et al. 2014) approach than by requisite one due to the purpose of the latter to approximate and simplify complex interactions (Phillips 1984).

Further, Lynch et al. (2014) argued that multiparadigm modelling offers benefits over single modeling because it allows interactions representation of system elements at all levels of granularity, by the most appropriate paradigm. That approach provides means for reducing approximation of system elements and their interactions, thus increasing the level of correspondence between the model and the modelled environment.

Table 2.5.2.1 provides a categorisation of SD and AB papers according to main topics and key gaps that have been identified, connected to their approaches to treating their main research questions. These gaps, while related to methods applied, could produce results and recommendations which could not take a comprehensive account of the complex adaptive system behaviour. This in turn, could provide support for policy decisions which do not fully reflect the system characteristics and thus could not provide optimal path for policy action and implementation (depending on specific policy objectives).

Table 2.5.2.1 Analysis of the reviewed research on system dynamics and agent-based modelling

Main topics	**Key gaps in the methods used**
SD: Application of system dynamic approach to the evaluation of pharmaceutical policy scenarios, related to: ○ High drug prices in public hospitals in China (Li et al. 2014) ○ Level of public reimbursement (Kazakov and Petrova, 2015) ○ Drug policy scenario simulation (Kunc and Kazakov, 2013) ○ Market competition structure and product launch pricing (Kazakov and Kunc, 2015) ○ High medicine price, price fixing due to doctor induced demand (Zhu et al., 2006)	**Lack of account of market agent behaviour and decision routine** **Limited theoretical support from a resource/agent behaviour perspective**
ABM: Application of agent modelling and simulation for the exploration of pharmaceutical policy: ○ Scenario analysis of public financing (Megido et al. 2015) ○ Incentives for behavioural change related to overuse of high priced medicines or underuse of lower priced generic drugs; Evaluation of financial incentives for cardiovascular drugs utilization (Tang and Rosen, 2014) ○ Chronic health clinical and policy relevant analytical review and recommendation for future work in CVD to include modelling the effect of drug therapy (Li et al. 2016)	**Lack of account for agent interaction with and competition for system resources** **No theoretical support from theoretical frameworks, including resource/agent behaviour perspective**

DE: Application of DE simulation modelling to pharmaceutical pricing policy Scenario analysis of external reference pricing regulation (Toumi et al, 2014)	**Lack of account of system agents decision pattern, and agent/resource and agent/agent competing interactions** **Lack of theoretical support from no theoretical framework, including resource/agent behaviour perspective**
Hybrid: Application of hybrid SD/AB simulation modelling Prospective HTA for mobile stroke units (Djanatliev et al. 2014)	**Limited account for the agent's behavioural decision rules in connection to agent resources interaction** **No theoretical support neither from a chosen theoretical framework , nor from a resource/agent behaviour perspective**

2.5.3 Research Gap Analysis

In regard to the ERP regulation analysis, main findings are, that neither system dynamic nor agent based modelling and simulation approaches have been applied, and no theoretical framework support has been used anywhere, regarding treatment of the pharmaceutical system and ERP from a resource/agent behavioural interaction perspective. No exploration of regulatory and market contextual interference on the ERP effects, and no comprehensive scenario analysis for the ERP regulation evaluation have been performed.

Analyzing the methodological application related to each pharmaceutical pricing regulation theme covered in the published papers above, there emerged a variety of important topics which appeared that have not been treated by any dynamic simulation modelling approach (Figure 2.5.3.1) alone or in combination. Application of such methods is advocated by Roberts (2015), Marshall et al. (2015a) and Marshall et al. (2015b) to be more appropriate to the treatment of complex health care delivery systems. High

relevant research questions pertinent to local and global (EU) pharmaceutical pricing regulation, which exploration can benefit by SD, AB and hybrid modelling are related to product price competition in an INN (MOLECULE NAME) or branded market, with or without product substitution legally allowed, internal reference pricing and generic competition, price linkage between the original reference and new generic product, differential pricing, fixed co-payment effect on product price, parallel trade, price related payback effect, tendering etc. In addition, external reference pricing (ERP), induced demand, price co-payment, product pricing, drug budget efficiency and pricing policy mix, have been examined by a very few dynamic modelling applications from only one methodological point of view (exhibiting limitations in scope, in technical capacity and in comprehensive perspective), and could further benefit from hybrid methodological approach which can bring opportunity for enhancement and enriched RQ exploration.

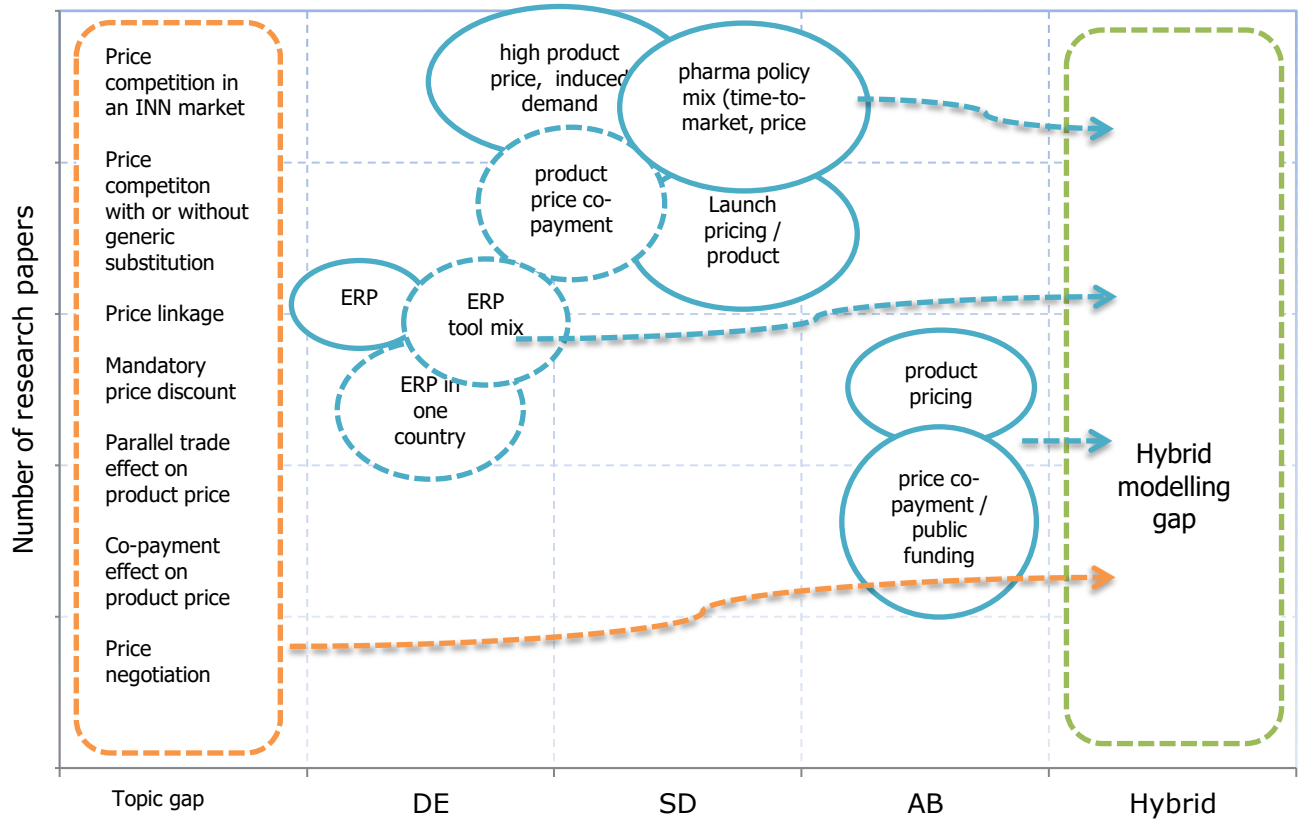


Figure 2.5.3.1 Modelling and Topic Gap Map

Legend: On the y axis is the number of research papers using DE, SD, AB or hybrid simulation modelling (these methods are shown on x axis, which includes also "topic gap"). The papers selected through the literature review are mapped on the figure against the two axis in blue circles, which are meant to show their number, main research topics and simulation methods used . The dotted line circles mean that these papers use one and the same simulation model to perform different analysis. Topics

included in the "Topic gap" box have been identified through the literature review as important but have not been treated with dynamic simulation methods. Arrows show which topics relate to the hybrid simulation gap.

However, a key gap regarding the evaluation of the ERP policy effect on equitable access to affordable medicines treatments on the EU markets, and medicine availability and affordability comes out of the fact that hybrid quantitative modelling and simulation approach to ERP policy evaluation has not been applied. Neither there has been applied any hybrid or individual qualitative modelling or mapping methodology. There has been applied no SD or AB modelling and simulation, and no theoretical framework support has been used anywhere, regarding treatment of the pharmaceutical system and ERP from a resource/agent interactive behaviour (Table 2.5.2.1). Regarding the ERP subject exploration, no exploration of regulatory and market contextual variation interference and mediation effect on the ERP has been made, neither any exploration for a flexible ERP regulation adequate to the local context. The importance and expected contribution of my PhD project will be related to the use of these approaches to address the comprehensive evaluation of the ERP regulation, and to address also the above mentioned multi-methodological gap, pharmaceutical pricing policy modelling gap, and the External reference pricing (ERP) modelling evaluation gap. This supports the need for concentration on and exploration of the following RQ (introduced in the beginning: "What are the effects of External Reference Pricing on EU pharmaceutical market systems in relation to equitable access to, availability and affordability of medicines?", applying SD and AB hybrid methodological approach.

The exploration of the RQ will focus on main challenges, accentuated by the European Council report:

- ERP effect on time delay in launching medicines (drug access criterion)
- ERP effect on excessive pricing of medicines (drug affordability criterion)
- ERP effect on shortages of medicines (drug availability criterion)

Analysing the effects of the ERP in regard to medicines availability (market delays and withdrawals), and affordability (high prices) requires taking account of system interactions among main resources and resource flows, and main agents behaviours. These are medicines stocks and supply chains on the local market, public budget resources and out of pocket money flows on one side, and on the other, market agents like companies making launch and price decisions, like prescribing doctors and buying patients.

In this respect, the treatment of the above RQ and related specific questions will require the application of an integrated conceptual (qualitative) and quantitative AB and SD modelling and simulation methodology, which can support comprehensive policy evaluation and optimal policy decision making.

In relation to the need of more "accurate" modelling practice (Ghaffarzadegan et al. 2011) in health care and pharmaceuticals, Roberts (2015) argued that complex systems like health care may need hybrid modelling and simulation approaches in order to be represented more "precisely", and that dynamic simulation methods had enormous potential to improve the efficiency of healthcare systems.

Policy decision makers need to understand complexities of the health care system context emerging from the agent and resource interactions. Improving the efficiency of health care including pharmaceutical complex systems would require dynamic simulation modelling approach to the evaluation of health care policies and anticipation of interventions effect, because agents have adaptive nonlinear decisions and actions changing over time, affecting resource levels and resource structures Marshall et al. (2015a).

Health care delivery systems including pharmaceutical sub systems and supply chain processes, have abundance of feedback, resource accumulations, resource flows, and time delays features in addition to autonomous and interacting agents. Hybrid modelling and simulation experimentation with different “what-if” policies can provide an interactive learning apparatus for assumptions testing, and anticipation of the effects of different system scenarios (Ghaffarzadegan et al. 2011; Kunc & Kazakov 2013; Kazakov & Kunc 2016; Kazakov & Petrova 2015; Marshall, Burgos-liz, et al. 2015; Marshall, Burgos-Liz, et al. 2015)

In that way policy decision makers are enabled “to anticipate the consequences of unforeseen interactions in the system (emergence) and become prescriptive in nature, such that the models prescribe what actions/interventions to take, on the basis of scenarios tested through experiments” (Marshall et al. 2015a).

Chapter 3 Philosophical paradigm

Chapter 3 presents a philosophical paradigm and its ontological adequacy from the perspective of the intended research on pharmaceutical systems. Pharmaceutical market and pricing regulation could be understood as a socio-economic and politico-regulatory

reality with implicit (not directly manifested) and explicit market dynamics, in which structural and emerging characteristics are being constructed by the interrelations among agent and resource structures involved in that system. A critical realist philosophical paradigm brings an alternative to the competing positivist and interpretivist related research methods and grants a larger ontological and epistemological field for the exploration of the emerging behaviour of complex pharmaceutical systems and the understanding of their internal dialectics, in relation to competitive agent/resource interrelations.

3.1 Philosophical Paradigm of the PhD project

Critical Realism (CR)/Dialectical Critical Realism (DCR) (Bhaskar 1989; Bhaskar 1998; BHASKAR 1978; Collier, 1994; Mingers 2000; Mingers 2006) provide the philosophical means for bridging the ontological and epistemological dichotomy between the extremes of positivism and interpretivism by overcoming their dialectical conflict. It provides an ontology of the real/actual/empirical, which corresponds to the complex socio-economic constantly evolving reality being an open system with non-linear emerging properties (Kauffman 1995; Anderson et al., 1999).

CR/DCR paradigm explains the real world as being stratified into different unified dimensions. These dimensions are the 'real', which exists but could be not active, i.e. latent and hidden from the observer; which could be 'actual' but still unobservable like underlying interrelations growing to emergent properties of a complex adaptive social system; and which could be 'empirical', i.e. having observable characteristics. CR/DCR admits that knowledge of the real could be intermediated by the observer's interpretation, values and beliefs. This approach builds on critiquing both positivist and interpretivist/constructivist ontology and epistemology to create a new philosophical paradigm, which takes into account that the previous two are not capable to comprehend the social realism in a full holistic perspective.

According to Gorsky (2013), CR "is ''realist'' in the generic sense that it takes a ''mind-independent'' nature as a fundamental ''condition of possibility'' for natural science. But it is also realist in the ''critical'' sense that it sees science as a human activity that is inevitably mediated (if not determined) by human language and social power." CR examines the relationship between science and ethics by an ''explanatory critique'', meaning that the scientific enquiry is not value free, which relates to the key idea of changing the reality for the better. According to Bhaskar (1986) "If one can demonstrate a systematic connection between inaccurate beliefs and oppressive social structures, then

one has not only explained the beliefs but also supplied a motivation for changing the structures. One has made the leap from facts to values." That CR attitude toward the social world around is relevant to the idea of the role of the public (health care and pharmaceutical) regulation to balance the interest of the public against the private economic interest, hence the need of regulatory change when it could not fulfil its public goal. Regarding pharmaceutical and healthcare regulation, ensuring equality of access to, affordability and availability of medicinal treatment and medical care are their ultimate purpose.

Bhaskar dialectic provides a relevant explanation of how complex social adaptive systems behave in relation to distinctness of resource structures in time; interacting agents across time; relations within and between agents and resources in systemic terms; and reflection for action, which have provided a reference point for a CR ontological and epistemological approach to complex adaptive systems research (Mingers 2000; Mingers 2006). Neither the dominant positivist/functionalist paradigm, nor the interpretivist one could be able to philosophically sustain the modelling of complex socio-economic systems and their dialectical interrelations (resources, agents, flows dynamics, cognition/decision making rules and patterns of behaviour bounded by information imperfections, and the emerging/emergent properties of the whole interrelated system);

According to the above, an ontological and epistemological perspective like CR/DCR which can encompass the different layers of reality /'real', 'actual' and 'empirical'/, would be relevant to support the explanation of complex socio-economic adaptive systems.

3.2. Pharmaceutical market systems from CR point of view

Another reason for the hybrid integration of both approaches is not related to their technical capacity to handle resource systems on one side and agent systems on another, but to the contextual representation of pharmaceutical markets as systems consisting of agents competing for limited resources. Naturally, a new guiding principle for the need of SD and AB modelling and simulation integration can be formulated to be linked to agent/resource rival symbiotic systems .

Pharmaceutical market eco-system viewed from the CR/DCR perspective could be understood as a socio-economic and politico-regulatory reality with implicit (not directly manifested) and explicit market dynamics, which knowledge about its structural and emerging characteristics is being constructed by the interested social groups involved in that specific eco-system (system containing sub-systems of resources and agents like government health care administration/policy makers, pharmaceutical original and

generics industry, doctors and pharmacists, and patients groups, all being key actors and decision makers influencing other agents' cognition, behaviour and flow of resources).

Figure 3.2.1 exhibit the ontological paradigm interrelations in terms of explaining the complex characteristics of the pharmaceutical market environment and the pharmaceutical policy evaluation research framework. In brief, the Pharmaceutical Market Eco-System contains N in number sub-systems of resources and agents' interrelations which produce its complex (independent from the observer) emerging 'Reality' (Figure 3.2.1). However, the nature of the knowledge about that 'Reality' is mediated by the cognitive prism of the actors (stakeholder groups) involved in its ('Reality') formation and unfolding. As the economy and markets are not perfect in relation to the information available (prices, product quality, etc.), all individual and group agents interact within an information asymmetry/inequality environment which can lead to Arrow's agency related phenomena (interest seeking behaviour or "moral hazard") and adverse selection (selection of less efficient choices) of alternative decisions (Arrow, 1976 ; Stiglitz, 2000).

The pharmaceutical market environment is characterised with scarcity of and dependence on available resources (budget, in-patent or off-patent medicines, qualified workers, distribution channels etc.) which is central for the dialectical relations between the socio-economic agents both from macro and micro perspective. In addition, agents make decisions which affect reality. Their decisions are constraint by bounded rationality, and influenced by the expected future result of their alternative actions, Anticipatory Systems Theory).

CR and further DCR provides a relevant philosophical environment for supporting the conceptualisation of pharmaceutical systems as complex social adaptive systems consisting of changing resource structures and interacting agents in time, and the need for analysing such systems in a critical way.

This philosophical paradigm offers ontological perspective for the theoretical framework supporting the hybridisation of SD and AB methods, which is further described in the next chapter 4.

Figure 3.2.1

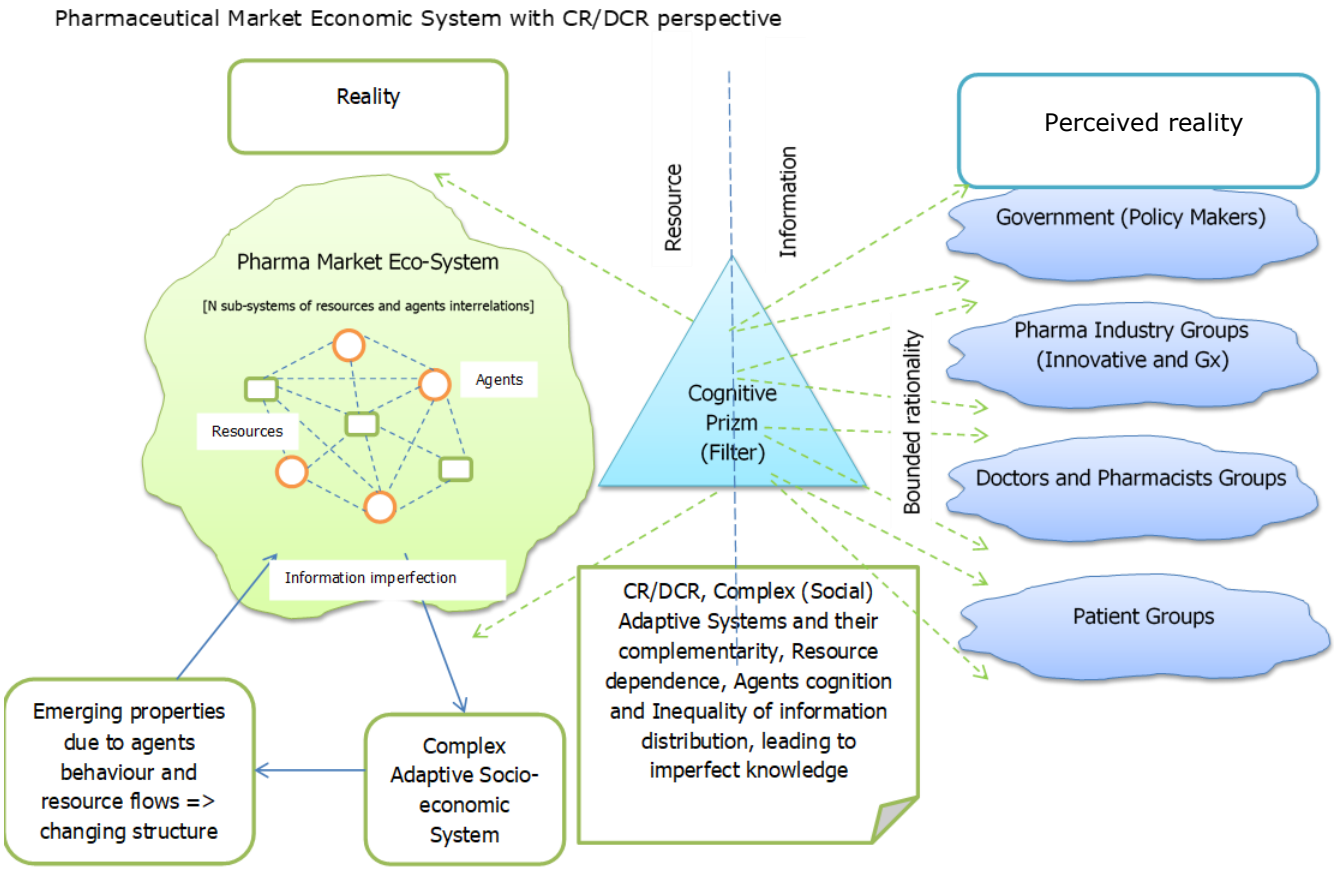


Figure 3.2.1 Pharmaceutical market system with CR (DCR) perspective

Chapter 4 Theoretical prism: Enhancing the theoretical framework behind the integration of System Dynamics and Agent Based modelling for use in pharmaceutical systems

Chapter 4 brings further explanation regarding the rich theoretical prism employed with the aim to clarify the theoretical argumentation for the hybrid modelling and simulation methodological framework applied to the exploration of the research question. Important concepts and economic behavioral phenomena central to the PhD project, like resources, agents, and imperfect information are clarified through the lenses of the Resource-based Theory, Resource Dependence Theory, Complex Adaptive Systems, Anticipatory Systems Theory, and Behavioral Decision Theory.

4.1 Introduction

A novel view for an integrative SD and AB modelling framework, ontologically connected to CR principles, explained in previous chapter, for use in pharmaceutical systems is proposed here. This is centred around the key concepts of resources and agents, and is supported by the theoretical perspectives of resource-dependence theory and resource-based view, behavioural decision theory, and anticipatory systems theory.

The effort to bring together in a unified theoretical prism, theories related to SD and ABM follows the idea that "alternative theoretical frameworks to provide practical guidance for multimethodology design need to be investigated" (Mingers & Brocklesby 1997). This idea is relevant to the challenge of "borrowing and developing theory to further our understanding of problem structuring practice" (Ackermann et al. 2014), and the challenge of "developing effective procedure for mixing methods" (Ackermann et al. 2014; Howick et al. 2008).

Research has been recently developed in the direction of the above challenges (Ackermann et al. 2014) but in relation to the integration of SD and AB modelling there hasn't been any advancement in developing a common unified theoretical frame behind the practice of the hybridization of both methodological approaches, capable to inform a generalized procedure for their effective mixing and integration. An initial discussion on their common and distinctive features, and benefits of combination of both methods has been put forward by a few researchers (Phelan 1999; Schieritz & Milling 2003; Schieritz 2002; Hans J Scholl 2001; Guerrero et al. 2016b).

Howick and Ackermann (Howick et al. 2008) also have identified the need for a good conceptual perspective and good theory supporting the practice of mixing OR methods by stating a need for: "...development of conceptual frameworks and ultimately theory – ensuring that Lewin's (1946) view that "there is nothing as practical as good theory" can be applied to the combination of different OR methodological frameworks.

The chapter focuses on developing a multitheoretical prism in support of combining SD and AB methodological techniques into a unified hybrid modelling and simulation research apparatus for the exploration of complex adaptive socioeconomic systems of resources and agents' interactions.

The resource/agent integrated conceptual framework proposed here contributes to the above outlined challenges and to ongoing efforts of the modelling and simulation community to develop an enhanced epistemological paradigm in support of the integration of SD and AB methodological approaches. Another practical contribution is the application of the conceptual framework to the call of the European Council for a systemic evaluation of the pharmaceutical regulation in EU and associated pharmaceutical market system effects, and specifically to my research question regarding ERP systemic effect evaluation on equitable access, affordability and availability of medicinal products.

The novel view for a joint SD and AB modelling conceptual framework furthers the ongoing calls and research (Guerrero et al. 2016a; H. Scholl 2001; Schieritz & Milling 2003; Schieritz et al. 2004) is proposed to be conceptualized through the theoretical perspectives of resource-dependence theory and RBT (Jeffrey Pfeffer & Salancik 1978; Hillman et al. 2009; Wernerfeldt 1984; Barney 1991; Peteraf 1993), behavioural decision theory (Kahneman & Tversky 1979; Kahneman 2003), and anticipatory systems theory (Butz et al. 2007; Pezzulo 2007 Rosen 1985; Louie 2010).

Each of the above theoretical perspectives provides different knowledge and explanations of socio-economic phenomena and integrating them provides a more holistic view for critically exploring and interpreting market resource and agent interrelated behaviour. Conceptualizing the pharmaceutical market as an anticipatory adaptive socio-economic system emerging out of agents' heuristic rules and forward-looking behaviour, competing for limited resources within an informationally imperfect market environment, would further complement the general systems and complex adaptive systems theoretical frameworks underpinning the practical integration of SD and AB modelling approaches.

4.2 Agents/resource conceptualization of complex adaptive systems

There is increasing attention to the conceptualization of health care and pharmaceutical markets as complex adaptive systems in the academic and practical world (Marshall, Burgos-Liz, et al. 2015; Sterman 2000; Kunc & Kazakov 2014; Kunc & Kazakov 2013; Kazakov & Kunc 2016a; Kazakov & Petrova 2015; Roberts 2015; Mahsa Keshtkaran 2015; Homer & Hirsch 2006; Hirsch et al. 2010; Wolstenholme 2009). However there are not many studies that identify how policy makers in the health care, and pharmaceutical field in particular, may understand how to influence, regulate, and manage healthcare markets as complex systems of competing agents in an imperfect environment of constraint resources with the purpose to balance the interests of all stakeholder groups, in parallel with maintaining economic and social sustainability (Marshall, Burgos-liz, et al. 2015; Marshall, Burgos-Liz, et al. 2015; Hirsch et al. 2010; Diaz et al. 2015; Luke & Stamatakis 2012; Li et al. 2016; Djanatliev & German 2013; Djanatliev & German 2016).

This research argues that health care and pharmaceutical markets must be viewed as complex anticipatory adaptive socio-economic systems (Holland 1992; Kauffman 1995; Dooley 1996; Anderson 1999), emerging out of agents' heuristic rules and forward-looking behaviour, competing for limited valuable resources within informationally imperfect market environment.

The main elements of health care and pharmaceutical systems are the related market resources (e.g. public budget, drug stock volume, drug price); agents (e.g. innovative and generic drug companies, government, doctors, pharmacy units and patients); and the level of information imperfection. Any of the above system components and their qualitative and quantitative features, and behaviour ,is explained by each relevant theory.

In systems science approaches, 'qualitative' modelling means making a non-numerical diagrammatical system analysis using methods such as cognitive and causal maps, stock and flow diagrams, resource maps. Quantitative modelling refers to using numerical (computational) methods for parametrization and simulation of the system dynamics model, including input numerical parameters and outcome numerical indicators.

Resources and their features are explained within the general systems theory (Von Bertalanffy 1972) , Resource based view (Barney 1991; Peteraf 1993) and Resource dependence theory (Jeffrey Pfeffer & Salancik 1978) . Agents and their features are explained by the Behavioural decision theory (Kahneman & Tversky 1979), complex adaptive systems theory (Holland 2010; Anderson 1999) and Anticipatory systems theory (Rosen 1985).

Main consideration regarding the understanding of the pharmaceutical systems and their dynamics and emergent behaviour, taking a resource/agent system interactive perspective, is that such understanding will remain partial if relying only on one of the theories for the explanation of any of the system components in isolation to the other. In order to be capable of a comprehensive perspective (Rosenhead 2006) on the whole picture of the forest (Schieritz & Milling 2003) including the trees, the above system elements need to be grasped in their interrelational activities.

To this need comes the proposition of a theoretical framework capable to explain the resource/agent structural coupling, employing the already mentioned theories in a unified approach.

Naturally, resource subsystems can be modelled within the system dynamics approach, while agent sub systems can be modelled within the agent-based approach. However, a hybrid complex adaptive system (driven through resource/agent interactions dynamics) like the pharmaceutical market would not be adequately modelled by either of the above dynamic system approaches alone (in isolation to the other). Therefore, a hybrid SD/AB approach will be capable to achieve mutual qualitative and quantitative complementarity and to account for the natural hybrid ontological structure of the intertwined resource/agent modelled system.

Additionally, a hybrid theoretical frame capable to support resource/agent modelling and simulation will provide for the design of a research apparatus capable to advance a more comprehensive perspective (Rosenhead 2006; Ackermann et al. 2014) of complex socioeconomic systems like pharmaceuticals, health care and many other.

4.3 Theoretical enhancement behind the integration of SD and AB modelling methods: An Agent/Resource modelling perspective

4.3.1 System Dynamics theoretical enhancement

System Dynamics (SD) practice developed following two key concepts of systems theory related to the feedback loops principle, and to the principle that system's stock structure drives system's behavior.

Forrester (1958) pioneered SD practice following two key concepts of systems theory related to the feedback loops principle, and to the principle that system's structure drives system's behavior. A main view behind the behavior of complex dynamic systems

identifies hidden endogeneity and feedback effects due to delay in time and bound rationality, leading to non-linear and often counterintuitive behaviour (Sterman, 2000; Morecroft, 2007). Hence, systems dynamics modelling practice tries to uncover the hidden mechanisms underlying the observed non-linear effects in the economic systems "instead of only treating their symptoms" (Forrester, 1958).

Main building blocks in SD modelling are stocks or resources (Richardson & Pugh 1981; Forrester et al. 1976; Wolstenholme 1999; J D Sterman 2000b), flows and auxiliary variables. The more complex a model becomes the harder it is for the modeller to maintain accurate representation of the modelled environment and to manage the model behaviour and outcome adequacy to the issue under exploration.

Understanding the endogenous and exogenous characteristics of organizational and market complexity, being a source of causal ambiguity, emergent behaviour and self-organizational dynamics (Morel and Ramanujan, 1999) is well advanced by general systems theory (Von Bertalanffy 1968; Andrew 2003) and the system dynamics field of research (Forrester, 1961; Forrester 1995; Radzicki & Sterman 1994; Richardson & Pugh 1981; J Randers 1980; Morecroft 1999; Sterman, 2000; Morecroft, 2007). Systems complexity comes from dynamic components and their nonlinear interactions which cause emergent behaviour, the reasons for which are hardly obvious. The more complex interrelations are among the systems internal and external components, the more ambiguous are the causes of the system behaviour and its self-organizational dynamics.

4.3.1.1 The Resource based Theory (RBT)

The Resource-based theory (RBT) of the firm (Wernerfeldt 1984; Barney 1991; Peteraf 1993) focused its analyses on the internal or introvert perspective to posit that firms' performance differences are based on a certain set of internal capabilities or unique organizational assets (Dierickx et al. 1989), or resources which should lead to sustainable competitive advantage only if they are 'valuable, rare, imperfectly imitable, and non-substitutable' (Barney, 1991, pp. 105–111).

RBT also posits that firms can be conceptualized as bundles of resources, which are heterogeneously distributed across firms, (Amit & Schoemaker 1993; Wernerfeldt 1984; Penrose, 1959) are dynamic and need to be managed (Helfat & Peteraf 2015; Sirmon et al. 2007)by dynamic capabilities which align, coordinate, reconfigure and renew the firms resource base (Teece et al. 2008).

RBT is recognized to fit SD theory and practice (Gary et al. 2007) by the use of similar central concepts like resources, stocks, accumulation etc. Also, RBT has supported theoretically the application of Resource Maps (RM) qualitative modelling technique by the use of SD stock and flows, and causal loops analytical instrumentarium (Kunc & Morecroft 2009).

4.3.1.2 Resource Dependence Theory (RDT)

The RBT gives an internalized resource management perspective to the competitive behaviour of the industrial organizations. However, an externalized perspective can bring further clarity and unity in relation to the conceptualization of market resources and how the organizations and market systems are dependent on them.

The external resource dependence perspective of RDT (Jeffrey Pfeffer & Salancik 1978; Hillman et al. 2009) can complement the internal perspective of resource management of RBT and can further develop more full understanding of the intra and inter organizational resource structure in pharmaceutical market systems

RDT (Jeffrey Pfeffer & Salancik 1978; Hillman et al. 2009) views the organization as being an open system, dependent on contextual contingencies in the external market and regulatory environment. External micro and macro-economic context influence organizational behavior and a key goal of market agents would be reducing environmental uncertainty and dependence on valuable resources through control over vital resources (Ulrich & Barney 1984) by reducing competitors' and institutions power over them, attempting to increase their own power over the others.

RDT can provide a vital knowledge frame of what are the resource dependent forces of organizational behavior on the market and how organizations take actions to manage external interdependencies in order to reduce uncertainty and interdependence on the larger socioeconomic system, including market regulation. Further to the above, integrating RDT with the resource-based view of the firm (Barney 1991; Wernerfeldt 1984; Barney 1986) can provide a complementary focus on resources, and may offer new insights into the organizational resource depending behavior, including controlling valuable, rare, nonsubstitutable, and limited resources from the external environment (Hillman et al. 2009). Learning from the RBT and RDT allows for a richer consideration of how organizations develop routine to control resource needs internally and externally (Hillman et al. 2009).

In the above perspective, I have extended the RM by gaining broader insight from the RDT, regarding the dependence of organizations on the limited resources in the socio-economic and regulatory environment, and regarding their competitive behaviour related to maintaining control over them. This follows from the concept that any market, including the pharmaceutical one, need to be conceptualized as a structurally coupled complex adaptive system of agents and internal and external resources .

4.3.2 Agent based (AB) Modelling theoretical enhancement

AB modelling and simulation practice and applications are traditionally supported by CAS theory to explain agent behaviour: According to Axtell (2000) AB modelling compared to traditional approaches to modelling economic systems could be a more viable approach when there are reasons to think in terms of agents. For example, these are the situations when the problem or the research question we need to explore, is naturally represented by a large number of agents which decisions and behaviors can be well-defined, and which can exhibit adaptation and change,. A very important feature of Axtell's AB modelling criteria is linked to the structure of the system which has endogenously emerging mechanisms governing its future evolution and is not dependent only on the past (Axtell, 2000).

Macal and North (2010) acknowledge that AB modelling could be linked to complex systems (Weisbuch, 1991) and complex adaptive systems (Kauffman, 1993; Holland, 1995) theory and exploration. They understand ABM as a set of "ideas, techniques, and tools for implementing computational models of complex adaptive systems" with the aim to reveal origin of self-organization, emergent phenomenon, and adaptation (Macal and North, 2010)

The behavioural rules, emergence and adaptation effect of agent behaviour are tightly connected with the theory of complex adaptive systems (CAS) which do not have a controlling centre and a fixed structure. Rather they are structurally coupled with their environment and exhibit a co-evolutionary emerging feature, i.e. as the result of decentralized bottom-up decisions and behaviour of individual entities or agents over time (Guerrero et al., 2016; Macal, 2010; Macal and North, 2006). Agents' decisions and behaviour "shape and change the state and structure of the system and react to the dynamic changes in the system, which can potentially alter their decision rules" (Guerrero et al. 2016).

Agents have decision rules and autonomous actions, and interact with their environment forming non-linear and feedback effect. (Epstein and Axtell, 1996; Bonabeau, 2002; Phelan, 1999; Phelan 2001). Agents' decision rules which govern agents' behavior are linked to a goal-oriented behavior related to achieving a certain individual benefit, guided by the Behavioural Decision Theory (BDT) principle of satisficing /criteria of accessibility, risk aversion, and anchoring and adjustment/ rather than maximizing a utility function (Kahneman, 1979) due to their bounded rationality, and incomplete knowledge (Simon, 1959; Jennings et al., 1998) and unequal distribution of information (Akerlof, 1976; Stiglitz, 2000). Interestingly, according to Phelan (1999) when agents coordinate their decisions to achieve common goals, a "collective intelligence" phenomenon may emerge According to Schieritz, N. (2002) the building blocks of AB modelling are the individual agent, agent behavioral rule, inner and intra agent feedback connection, adaption of agent behaviour, inductive inference from individual agents' behavior to system behavior and discrete or continuous time frame. The agent pattern of behaviour or schema is "a cognitive structure that determines what action the agent takes at time t, given its perception of the environment" (Anderson, 1999) and can change or evolve in order to adapt to the agent environment.

However, modelling agent behaviour routine or schema should account for the agent "cognitive structure" and a relevant theory for the agent behavioural decision making and cognition principles is needed. Behavioural decision and Anticipation theory can enhance the practical understanding and explanation of agent behaviour and condition/action decision making.

4.3.2.1 Behaviour Decision Theory (BDT)

Simon, H. A. (1982; 1959), Kahneman and Tverzky (1979) and Kahneman (2003) can provide fruitful theoretical underpinning in support of AB modelling practice in a complex adaptive socio-economic paradigm. Market agents being they individual or organizational follow certain behavioural pattern informed by their cognition /perception of the environment/ and decision making which are rationally bounded due to incomplete information and imperfect cognition related to two types of cognitive processes, labeled by Stanovich and West (2000) System 1 and System 2 (Kahneman, 2011).

Kahneman offers a typology elaborating that the cognitive operations of System 1 are "fast, automatic, effortless, associative, and difficult to control or modify" while the

operations in System 2 are "slower, effortful, and deliberately controlled; they are also relatively flexible and potentially rule-governed

People behave following heuristics principle in order to reduce judgment and choice complexity (Tversky and Kahneman, 1974) like the principle of "availability", "anchoring and adjustment", "representativeness", "loss aversion" (Kahneman and Tversky, 1972; Kahneman and Tversky, 1979). According to Simon, people tend to make decisions by "satisficing" heuristic rather than optimizing a utility (Simon, 1956). Heuristics can also lead to cognitive biases (Kahneman, 2003). "Recognition" is another heuristic which simplifies decision making and makes best use of the limited information available to individuals (Goldstein, and Gigerenzer, 2002).

The BDT can inform the modelling of agents' decision making and their behaviour providing a scientific explanation of the pharmaceutical market agents' behaviour in relation to the ERP effect evaluation. Pharmaceutical companies make decisions which are rule based and also follow heuristic principles rather than utility maximization. BDT can help a better and more realistic modelling of their competitive behaviour including reactive or prospective activity in relation to drug price control mechanisms.

In relation to the above, Agent behavior modelling would need to account for each principle of BDT and relate to forward-looking behavior in an information imperfect market environment.

4.3.2.2 Anticipatory Systems Theory

Anticipatory systems theory posits that "anticipation is the process which enables a living system to contain a predictive model of itself and its environment. This allows it to adapt by changing its state in accordance with the model's predictions" (Louie 2010; Rosen 1978; Rosen 1985) and to base its course of actions on their anticipated effects. In cognitive science, anticipation is a core cognitive process responsible for the mental simulation of the would-be effects of human interaction with the external environment (Butz et al. 2007; Butz & Pezzulo 2008; Pezzulo 2007; Pezzulo 2008).

The cognitive process of anticipation is connected to building mental models of the external environment and simulating alternative actions and outcomes, where actions are triggered by the anticipated (mentally simulated) effect associated with their outcome, depicted on Figure 4.3.2.2 (Pezzulo, 2008). The agent possesses a forward model of the reality which includes agent´s future actions and their outcomes as anticipated by the

agent. This forward model is used as a reference to which the agent aligns their decisions for action. At the same time, the anticipation process requires also a 'controller' function which is the comparison of agents anticipated actions' outcomes and their actual outcomes. This 'controller' function serves like a comparative alignment mechanism for agents adaptive behaviour.

Butz et al. (2008) expand the definition of anticipatory systems with their ability to exhibit apart from "sensory" anticipations, "payoff" anticipations and "state" anticipations. Payoff anticipations are pertinent to systems that "have knowledge of behaviourally-dependent payoff and can base action selection on that representation, i.e. "different payoff may be predicted for alternative actions, which allows the selection of the current best action." State anticipation is based on anticipatory processes which enhance behavioural decision making by future anticipatory representations of not only the goal but of the whole system.

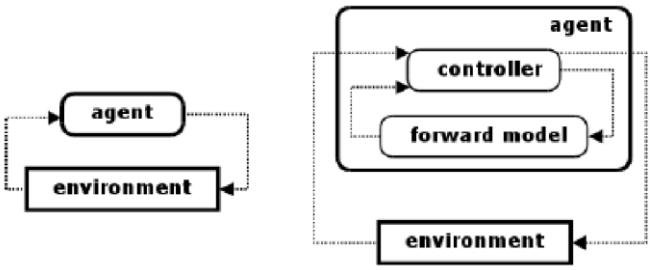


Figure 4.3.2.2 Anticipation and Anticipatory Process in Anticipatory Systems, containing forward model of agents' actions (Adapted from Pezzulo, 2008)

In relation to drug pricing regulation, regulatory authorities apply pricing control policy anticipating that prices would become more affordable and that the public interest/return would be optimized. However, pharmaceutical companies anticipating the behaviour of the pricing regulators react proactively in order to optimize their private interest/return and apply international pricing strategies in order to offset any unwanted effect. (Meyer & Szirbik 2007) stress the importance of state anticipation ability of organizations, which leads to emergent behaviour of the whole system "as predictions about future states directly influence current behavioural decision making".

Anticipatory systems perspective posits that agents and organizations build "forward models" of themselves (Pezzulo, 2008) thus simulating different paths ahead with different outcomes. Applying an anticipatory theoretical perspective to mapping agent behaviour can complement the complexity and behavioural perspectives to agent decision making analysis.

4.4 Application of the resource agent conceptual framework for the analysis of pharmaceutical market complex adaptive systems

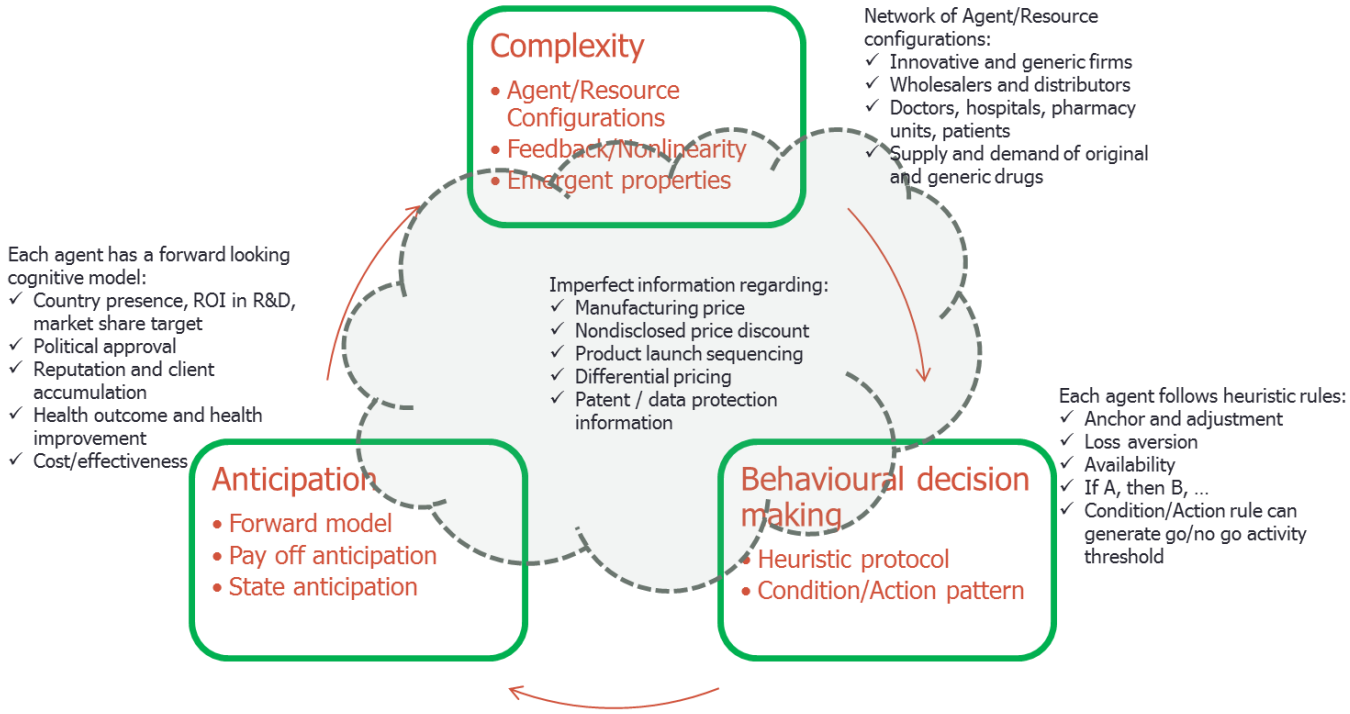


Figure 4.4.1 Agents competing for resources, and imperfect information as main features of socioeconomic Complex Adaptive Systems (CAS)

Figure 4.4.1 represents the pharmaceutical market complex system through the resource agent theoretical framework described so far, which later in Chapter 5 will be considered as main components of a novel Resource Agent framework. Markets and in particular health care and pharmaceutical markets (Roberts 2015; Marshall, Burgos-Liz, et al. 2015) are complex adaptive socioeconomic systems and agents and resources are key part of their complexity. All agents behave in parallel competing for control over firm and market resources in an adaptive manner, subject to a condition action rule pattern (Holland 1992; Holland 2006) and heuristic protocol of decision making (Kahneman & Tversky 1979, Simon, 1978), following a forward looking pay off or state anticipation behaviour.

Agent and resource configurations produce feedback, nonlinearity and emergent properties of the systems where information is imperfect and not equal available. Innovative and generic drug companies, wholesaler and distributors, hospitals and doctors, pharmacies and patients are actors in the supply chain of medicinal resources and follow commercial, societal or individual goals.

Agents can adapt/alter their pattern of behavior by deliberate action in order to fit to an observation or can take action to adapt an observation to their existing schema. Schema can change purposefully or randomly or by combination with other schema in order to adapt to the environment. Agents communicate/interact through exchanging information and or resources, which can have multiplier effects due to the interconnectedness in the system with flows that may be nonlinear.

Resources and agent interactions form complex systemic behaviour emerging out of resource/agent (R/A) configurations with feedback and non-linear inter and intra-configurational dynamics. R/A configurations in turn can also form further higher-order configurations by interacting further between themselves and forming higher-order feedback loops.

Apart from the large number of interactive elements, complex systems have also emergent properties, i.e., causal relations and feedback loops lead to the appearance of patterns or emergent structures (or constellations) of tightly coupled components. Managerial decisions are more or less concerned with discovering courses of action that satisfy a whole set of constraints, rather than maximizing a fitness function, which is consistent with the bounded rationality property of individuals and organizational systems (Simon 1978; Barros 2010; Jones & Jones 2002; Simon 2000; Simon 1972; Bendor 2010; Morel & Ramanujam 1999). Such behaviour is known as "satisficing" as opposed to the maximizing rational behaviour, and is subject to certain behavioural decision rules explained by the utility theory (Kahneman 2003a; Kahneman & Tversky 1979; Kahneman 2003b).

The proposed theoretical framework is illustrated in the context of the price control regulation on the pharmaceutical market in EU. The analysis focusses on the relevant market agents and market resources and related phenomena that could lead to market imperfections and market failure from the public healthcare perspective of providing equitable and timely access to affordable medicinal products.

Figure 4.4.2 provides information on how the theoretical framework can support the methodological framework bringing together system dynamics and agent based simulation modelling methods.

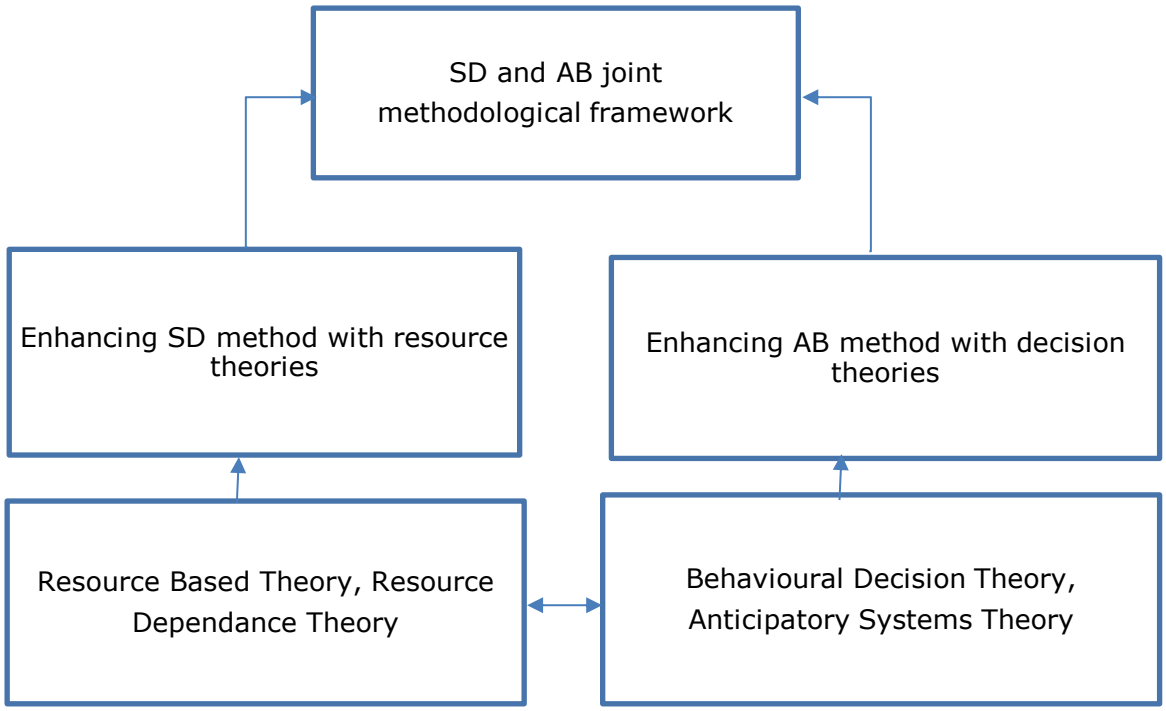


Figure 4.4.2 Theoretical framework supporting joint SD and AB methodological application

The Resource Based Theory and the Resource Dependance Theory are combined together to enhance the appreciation of resources within System Dynamics. The Behavioural Decision Theory and the Anticipatory Systems Theory are combined to enhance the decision making perspective within Agent based simulation method. Applied together they form the theoretical framework, supporting the combination and application of the above two distinctive methods.

Chapter 5 Methodological Framework: Managing pharmaceutical market systems by Resource/Agent Maps (RAM) and hybrid SD and AB quantitative simulation

5.1 Approach

The methodological approach I have employed can be summarized in Figure 5.1.1, which presents information on the main stages (qualitative and quantitative) and their related steps in the form of a resource agent modelling staircase.

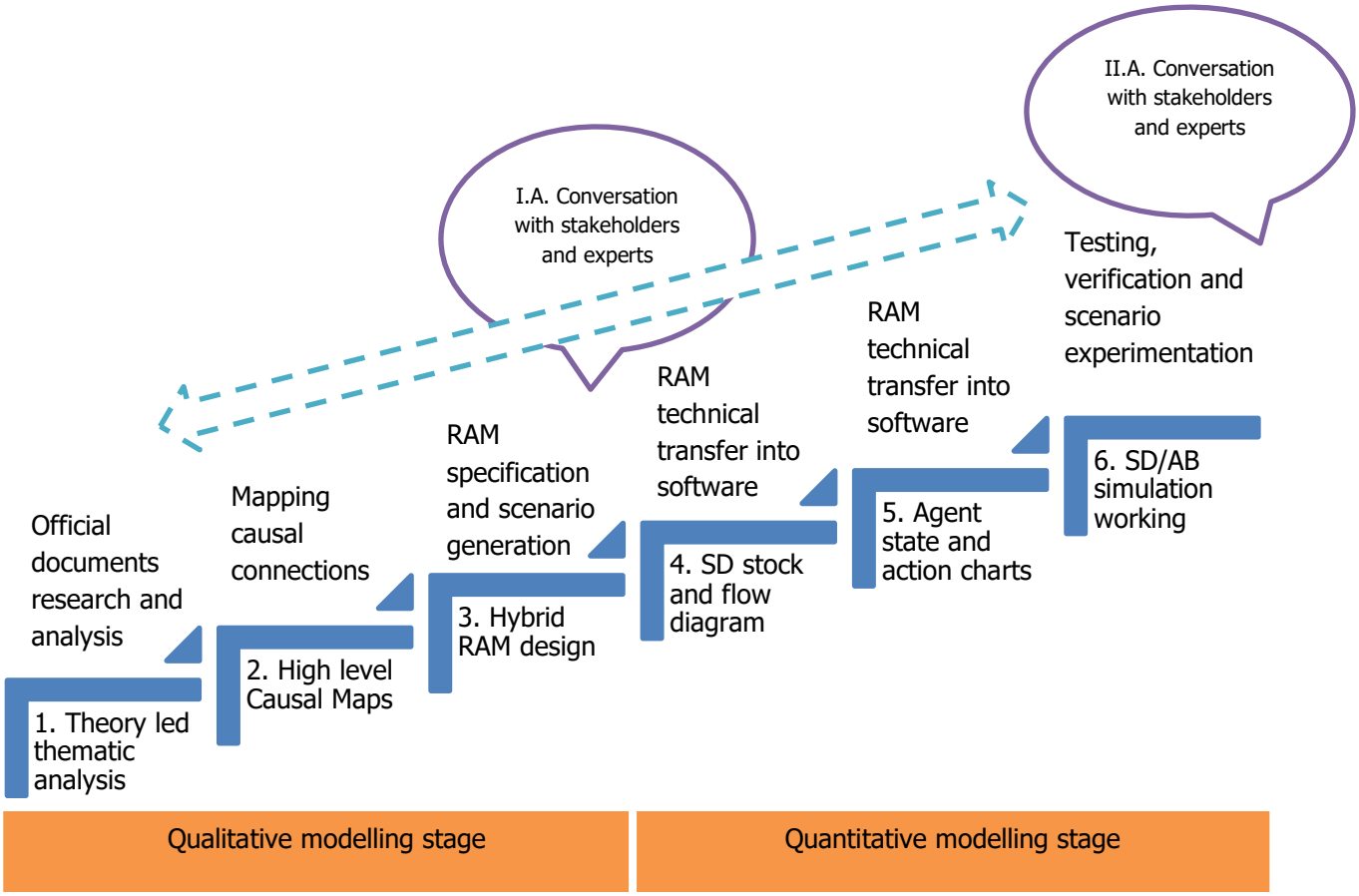


Figure 5.1.1. Confidence building procedure for the ERP simulation modelling

I. Qualitative Modelling Stage

The first stage was connected to gaining confidence in the conceptual (qualitative) modelling phase and consisted of the following steps:

1. Collecting and analysing qualitative information for the building of a conceptual qualitative model of the ERP effect on the market

Information regarding the ERP context was collected through written documentation output such as the EURIPID report (Schneider 2017), pharmaceutical industry position letters, author observation and participation in drug industry working group meetings and meetings with health care regulatory authorities. The goal was to use the data collected from document analysis (Barr et al. 1992), minutes of meetings and industry position papers (Huff & Schwenk 1990; Barr et al., 1992), conversations, researcher notes and reflection (Ackermann 2012; Ackermann & Eden 2011; Eden & Ackermann 2004), for the mapping of mental models (Doyle & Ford 1998; Carley 1997; Jones et al. 2011) of key stakeholders in the pharmaceutical market, i.e. the pharmaceutical industry and drug pricing regulators.

To extract relevant information, I have used a theory led thematic analysis (Hayes 1997) protocol, consisting of looking for, and elucidating, meaning connected to the following themes:

- Key resources and key agents in the pharmaceutical market system;
    - Textual analysis for the identification and categorization of main resources and actors in the system
- ERP regulation effect on the pharmaceutical market system, in relation to drug access, affordability and availability;
    - Textual analysis for identification of main assertions regarding ERP effects on drug access, affordability and availability
- Key agent/resources and agent/agents interrelations, including the main influencing factors affecting resource levels and flow rates and agent behavioural routines;
    - Textual analysis regarding agents' behavioural routines and how these influence on main resources levels and vice versa
    - Textual analysis regarding main actors' interrelations influencing their behavioural routines
- Key agents and resources behaviour in relation to ERP regulation and other contextual pricing and market regulation;

        - Text analysis regarding ERP and other relevant local drug regulation influencing agents' behavioural routines

    - Agents' behavioural routines (agents' "if/then" condition action rules), in relation to the effect of ERP on their pricing strategies

        - What are agents' decision and action patterns in response to ERP regulation

The main information sources and insights are shown in Table 6.1.A. The information extracted from these sources was categorized in two further tables (Table 6.1.B and Table 6.1.C), which describe the key resources and agents identified in addition to their related influencing factors.

2. Creating cause maps to highlight the key conceptual interrelations among the main systems components following (Howick et al., 2008; Kim and Andersen, 2012)

The next step was related to creating causal maps connected to the thematic purposive textual analysis performed in the first step, which was done through representation of main resources, agents and documented assertions regarding their interrelations in respect to the ERP and local contextual regulation into the graphical format of a causal map (provided examples in Chapter 7 on qualitative Resource Agent Maps (RAM)).

Their purpose was to support the transfer of the textual analysis of the ERP system's resources and agents, and their interdependence into a RAM.

3. Moving on to the transfer the cause maps into resource agents' interrelations through design of an enhanced Resource Map, an Agent Interaction Map and an Agent Behaviour Map for the purpose to create a RAM.

Validation of the maps involved the following procedure. Firstly, when building the maps, the content of each map (resources, agents, agents' rules and interconnections) was an "understandable and tight description of how the "world" works" (Howick et al. 2008) since they come from documented stakeholders' statements related to the above concepts and related to the functioning of the ERP regulation and its effect on drug access, affordability and availability in EU.

Secondly, documented stakeholders' statements (innovative and generic drug companies, health care regulators, drug pricing experts) were taken to be valid representations of their mental model (understanding) about the above, since they are

used in official position papers, meeting minutes and journal publications (Huff & Jenkins 2002; Carley 1997), and are taken as 'purposive' text (Kim and Andersen, 2012)

I.A. Conversation with Stakeholders and Experts

Conducting conversations to provoke and collect expert opinion on the capabilities of the conceptual model (RAM) to provide a correct and trustful representation of the real functioning of the market system in connection to the ERP effects on drug access, availability and affordability

The procedure for creating the resource agent maps was first explained and generated scenarios were presented to stakeholders' representatives and independent experts in the ERP drug pricing regulation and pharmaceutical markets (Eden & Ackermann 2004; Howick et al. 2008). Validation of the maps followed a conversation approach for ensuring "legitimacy and rightness" (Franco, 2006) in relation to gaining agreement (Mingers and Rosenhead, 2004) on the representation of the maps' interconnected elements. The conversation was conducted through semi-structured interviews that focused on key resources, agent behavioural rules and their interrelations represented on the maps. The conversational approach was performed with three groups of pharmaceutical market and regulation experts: independent experts, representatives of the medicine's companies and representatives of drug pricing authorities. Each group consisted of three or more experts coming from different countries and nationalities and with diverse educational and professional backgrounds. The experts were selected through approaching industry associations, public authorities and independent organisations, like Medicines for Europe (MfE), Federation of Innovative pharmaceutical Manufacturers (EFPIA), European Medicines distributors Association (GIRP), Bulgarian pharmaceutical Association (BGPharmA), Bulgarian pricing Commission, Austrian Institute on Pricing (ÖBIG), networks of individual experts like linkedin. Their job functions included market access managers (MfE and EFPIA), regulatory managers (GIRP, BGPharmA), medicines pricing experts (Bulgarian pricing commission, Austrian Institute on Pricing), experts and independent consultants (former senior managers who have worked for pharmaceutical companies).

Conversations were conducted through meetings on site or online, using a list of supporting questions (Appendix C), with the main goal to get experts evaluation opinion on the qualitative maps.

One of the conversations was conducted in the form of a workshop with participants with common research interest in the problem of drug availability and drug shortages

(Information about the workshop, participants and notes is included in Appendix C to chapter 6). After the workshop, subsequent follow up conversations were scheduled and conducted with selected participants who were interested in the ERP simulation modelling outcomes.

A summary of the expert's opinions and analysis of their perception of the RAM are presented in a Table 6.3.1 and in Appendix C to chapter 6. This supported elaboration of the RAM through taking into account relevant comments and opinion and suggestions to further correct and or enhance the components of the resource map and the agents maps and their combination into a RAM.

II. Quantitative Modelling Stage

The second stage was connected to ensuring confidence in the quantitative simulation phase and consisted of the following steps:

- Using the validated RAM as a hybrid simulation modelling procedure to transfer the qualitative representation of the resource agent system into a quantitative one
- Transferring the elements of the RAM into the chosen software environment, keeping their resource and agents' behaviour characteristics conceptually configured through the validated RAM
- This involved creating an exact quantitative structural and behavioural representation of the RAM within the used software

The first step of the quantitative stage consisted of transferring the resources and related components into a coded stock and flow charts and associated variables, while the second step included transfer of the agents and related components into coded agents state charts and behaviour algorithms, matching the conceptualized ERP system through the RAM.

Throughout the above procedure the quantitative simulation model was continuously tested to ensure methodological consistency and robustness in performance outcomes.

After the simulation model was built, it was tested with real drug prices for a number of selected drugs, obtained from Bulgarian price regulator and from EURIPID project drug price data initiative with the purpose to ensure that the simulated behaviour is reasonably similar to historical price evolution, meaning that the simulation model resources and agent's behaviour patterns are correctly configured, presented in Chapter 8 and in Appendix E to that Chapter.

ERP parameter variation and ERP policy scenarios experiments were conducted as a next step. The main purpose of the scenario experimentation was to increase confidence in the simulation performance and explore the ERP effects in connection to the research question. The simulated scenarios outcomes were compared to statistical public price evolution data which was obtained from the EURIPID project consortium. The simulated scenarios outcomes were compared also to previous ERP simulation studies and to ERP system analysis and observations published in official documents and journal papers.

Real and simulated drug price evolution of innovative and generic atorvastatin, clopidogrel and ticagrelor are compared in Chapter 8 for Bulgaria, Austria, Poland and other countries. Real public price data is obtained from the Bulgarian state committee on pricing and reimbursement and from EURIPID project drug public price data base.

II. A. Conducting conversations with interested parties to provoke and collect expert opinion on the quantitative simulation modelling outcomes and selected scenario experiments. The main purpose of the conversations was to understand to what level the participants recognize the presented simulated scenario outcomes to be trustful representation of the real ERP scenario effects. Or, of their expectations of the effects if similar ERP scenarios could occur in practice, due to hypothetical changes in the ERP regulation.

The conversations were performed with the same groups of experts following the same procedure performed for the RAM confidence stage. The interview questions with the researcher's notes are included in Appendix VI. A Table with a summary of the experts' opinions and analysis of their perception of the simulated ERP scenarios are included in chapters 7 and 8.

In relation to the RQ associated outcome, the three criteria of drug access, availability and affordability are measured as simulated ERP scenario outcomes. The first outcome is associated with how long a drug launch delay there is in relation to its entering a local market. The second outcome is associated with the average drug presence in years on a local market before this drug is being withdrawn from that market. The more years a drug is present on a market, the higher is that drug availability and vice versa. The third outcome of the scenario simulation is associated with the drug´s price evolution. The higher the price of a drug, less affordable is that drug. The quicker the price of a drug decreases, the higher becomes that drug´s affordability and more affordable is that drug to patients and healthcare funds.

Chapter 6 Collecting information to support a hybrid RAM qualitative and quantitative SD/AB modelling and simulation

Chapter 6 provides explanation of the qualitative and quantitative data that have been already collected, and the process used regarding the data collection, categorization and analysis.

Chapter 6 includes tables which have been published in a journal paper, coauthored with prof. Susan Howick and prof. Alec Morton, specifically Table 6.1.A, Table 6.1.B and Table 6.1.C (Kazakov et al., 2021)

6.1 Collecting relevant qualitative information

In collecting the needed information, I have adhered to a data collection plan related to defining, getting access to and analyzing the needed qualitative and quantitative data according to the research question (detailed plan included in Appendix VI to this chapter).

In addition to the review of prior published research on ERP, rich information regarding the ERP context has been collected through written documentation output. Documentation included working groups on ERP meeting minutes, EURIPID reports, official industry and government position papers, and European Commission project reports. The goal was to use the collected data from document analysis (Barr et al. 1992), minutes of meetings and industry position papers (Huff & Schwenk 1990; Barr et al., 1992), conversations, researcher notes and reflection (Ackermann 2012; Ackermann & Eden 2011; Eden & Ackermann 2004), for the qualitative modelling of the ERP research question in order to produce pictorial representation of data (Huff 1990; Eden 1988), by the use of enhanced Resource maps and the novel Agent maps techniques presented in the previous sections. Conversations include conducting in person and online meetings with three groups of experts (as described before), during which expert opinion was noted down in researchers notes and used through reflection in support of confidence building in the qualitative and quantitative simulation modelling stages.

The abovementioned group of experts included representatives of industrial associations like BGPharmA (Bulgarian Pharmaceutical Association), MfE (Medicines for Europe) and EFPIA (European Federation of Innovative Drug Associations), independent experts (drug

market professionals) and representatives of drug regulation authorities (Bulgarian National Price Regulation Council).

I used a theory led thematic analysis approach (Hayes 1997) in order to extract relevant information from the documentation output, consisting of looking for and elucidating meaning connected to the following key themes:

- Key resources and key agents in the pharmaceutical market system;
- External reference pricing regulation effect on the pharmaceutical market system;
- Key agent/resources and agent/agents' interrelations, including main influencing factors;
- Key agents and resources behaviour in relation to ERP regulation and other contextual pricing and market regulation;

Influencing factors (included in Table 6.1.B and 6.1.C) relate to factors that have an influence on the resource dynamics or on the agent behaviours. For example, the resource levels related to the pharmaceutical products stocks and flows in the drug supply chain, are influenced by the drug manufacturers agents (decisions and behaviour), the level of demand and supply (local market competitors), drug´s price. Influencing factors that have an effect on the agents decisions are, for example, local drug prescribing and drug pricing regulation, level of competition (supply) and level of demand (drug quantities consumed), parallel traders activity and other.

The information extracted from the data sources was categorized in three tables consisting of key stakeholder assertions regarding the ERP regulation effect on the pharmaceutical market, and description of key resources and key agents, including related influencing factors (Table 6.1.A, Table 6.1.B and Table 6.1.C).

All of this information and its sources are publicly available and can be easily tracked back and reproduced by interested researchers, including the assertions listed in these three tables.

Table 6.1.A ERP information sources and key assertions regarding the ERP effect on the pharmaceutical system

Information Source	**Goal**	**Key assertions regarding ERP effect**	**Documentation record**	**Timing**
ERP working group member at a European	To analyse and define generic and innovative	Negative impact on the pharmaceutical industry competitiveness (off-patent generic and	Memorandums, meeting minutes, official position papers, email	2015 2016 2017 2018

medicines industry association **Official innovative and generic industry associations position papers**	industry official position	biosimilar or in-patent medicine industry); From the European Generic medicine Association (EGA) perspective, and considering the very competitive environment of off-patent medicine market, ERP limits generic medicine industry's potential to enter specific markets by driving down the prices to unsustainable levels; referencing prices in countries where procurement and tendering systems are in place (driving down the prices to unsustainable levels) would be detrimental for the generic sector, for patients (availability of affordable generic medicines) and for payers (savings for the national health systems); From the European Federation of Pharmaceutical Industries and Associations (EFPIA) perspective, ERP causes indirect and adverse effects across Europe and beyond, especially in the	correspondence; observer notes	

		context of short-term cost-containment measures; ERP and parallel trade created spill-over effects from low price to higher price countries leading to patient access issues in low price markets, with limited benefits in terms of cost-savings to payers and patients for high price markets;		
Board member and Price Regulation task force member at a national drug industry association	To analyse and define BG industry position	ERP can lead to unsustainable price reduction for generics locally and abroad in cross referenced countries, and to product delay or delisting from reimbursement; Need to apply a more balanced price calculation formula and reference country basket	Like the above	2015 to 2018
Meetings on the topic with authorities, decision makers and experts	To understand health authorities position and build consensus	ERP is effective mechanism for price reduction; Need more price information transparency among reference countries	Observer notes	2015 to 2018

Prior research analysis	To analyse previous findings	Provided in Tables on the ERP related literature review	Literature review	2010 to 2018

Table 6.1.B Key Resources identified relevant to ERP.

Internal and External Resources	**Description**	**Influencing factor**
Medicinal product	Medicinal products are a key resource and are related to demand and supply side of the pharmaceutical market Critical attention of the healthcare authorities is directed to guaranteeing drug timely access, affordability and availability	Manufacturing agent Level of demand and supply Product price
Product official price	Product price is a resource connected to economic rent for the manufacturers and suppliers, and to economic expenditure for the healthcare funds and consumers Critical attention of the healthcare authorities is directed to contain drug expenditure by reducing product max allowed price	Pricing regulation Government Manufacturing agent
Product market price	A competitive price formed after a discount is given off the official price to the payer and distribution agent	Government and Manufacturing agent Competition
Doctors	Key for drug prescribing volume and drug allocation Pharmaceutical companies compete for control over that resource	Manufacturing agent and Prescribing regulation, i.e. by innovative or generic

		brand or by INN (MOLECULE NAME)
Patients	Key for generating product demand	Doctor agent and prescribing regulation
Public drugs budget	Key resource supporting product demand and supply Critical attention is directed to its distribution among drug categories through different level of reimbursement	Healthcare fund Reimbursement regulation, Product demand and product supply
Drug price information	Important for price elasticity level and product switching	Government Agents along the supply chain

Table 6.1.C Key Agents identified relevant to the ERP

Agents	Description	Influencing factor
Innovative companies	Main market agents producing original drugs protected by patent and data exclusivity	Price regulation and Competition Level of demand and Parallel trade
Generic drug companies	Main market agents manufacturing the same drug molecules after patent expiration	Price regulation and Competition Level of demand
Government	Main agent setting the pricing regulation on a local market	Limited drug budget Level of demand and supply
Doctors	Main prescribing agent	Companies detailing Other incentives

Pharmacy units	Main dispensing agent	Financial incentives like discounts
Patient	Main consuming agent	Prescribing doctors and Pharmacists

The main objective of the information collection and then the application of RM and AM was to extract and map stakeholders conceptualization of key resources and market agents, categorize them in their capacity to be key elements of the market system responsible for its emerging dynamics, analyze causality interrelations endogenous to the system, and elicit key insights about endogenous systemic dialectical interrelations for problem structuring in accordance with key principles of the mapping process like surfacing, mapping and analysis (Bryson et al. 2016; Jenkins 1998; Eden & Ackermann 1992; Eden & Ackermann 1998; Bryson et al. 2007; Ackermann et al. 1992).

Table 6.1.A provides a concise look at the information sources on ERP analysis and ERP market effect assertions of key stakeholders, which later were used to inform the RM, AM and RAM process. Table 6.1.B and Table 6.1.C present brief description of the key important resources, market agents and influencing factors, related to the ERP regulation in the pharmaceutical market, which set the endogenous system boundary of interacting resources and agents for the creating of the RM and AM. The process of resource, agent, and integrated resource/agent mapping was iterative and included various versions of the maps, due to the received feedback from experts and authors reflection on the maps and the data analysis. Previous versions of the maps and explanation of this procedure are included in Appendix VII and in Chapter 7.

Relevant data about national and EU Pricing & Reimbursement regulation rules is checked through using data sources on local legislation affecting the application of the ERP by local authorities. That data is linked to:

- Which countries are included in the price referencing group
- What product price do countries benchmark to (manufacturer or retail)
- Which product do countries apply the price referencing to (innovative, generic, publicly financed only or all)
- How do they determine the product price (price methodology of the lowest or the average price), and how often do they apply the price referencing (price revision period)
- What percent of reimbursement is applied by the local government, and what Price mark-up percent range in the supply chain

- What Prescribing and Dispensing regulation are there, for example, prescribing by INN (MOLECULE NAME) or prescribing by innovative or generic brand name, is generic drug substitution at the pharmacy allowed or not
- Is there information available to patients about product price alternatives in one INN (MOLECULE NAME) group

6.2 Collecting Quantitative data

The quantitative data that will be needed for the modelling and simulation stage and numerical validation will be related to the selected product markets, mainly regarding product prices evolution across EU ERP countries. For comparison reasons, a group of ERP countries will be used. Those selected were based on data availability that can support drug price evolution comparisons. Additional data about product market performance volumes and value (if available) can further be used for additional validation through calculating market prices and comparing with simulated output. The price data have been received (after delay due to agreement negotiation) by the EURIPID consortium which manages the EU wide drug public price data base. Also, public product price data has been obtained for the Bulgarian market through national pricing authorities. Additional relevant information about the local pricing regulation and the selected cardiovascular drugs prices, have been checked from national price regulatory and health statistical authorities.

The data needed relate only to researching ambulatory care and not the hospital market. In addition, only oral medicines that are not biological medicines or biosimilars are considered in the ERP simulation scenarios.

Specific information about the selected drug therapeutic categories is included in Table 6.2.1

Main reasons regarding the selection of these drugs and therapeutic categories are related to the following:

- Worldwide significance of the cardiovascular diseases (CVD) for the healthcare systems and wellbeing of treated patients, CVD remaining leading cause for disease burden in the world (www.who.int)
- CVD drugs are representative for the worldwide drug use and need for equitable drug access, affordability and availability
- CVD drugs are representative for the high degree of market competition

- Assumptions that data will be available for wider group of ERP countries

Table 6.2.1 Selected drug therapeutic categories

Case study in the following innovative and generic drug categories	**EU Countries**
1) Cholesterol lowering market (Atorvastatin)	Bulgaria and other EU member countries depending on data availability and comparability (EURIPID and national statistical data sources)
2) Innovative drugs (Alirocumab and Ticagrelor)	
3) Antiplatelet medicines market (Clopidogrel)	

Chapter 7 Qualitative Modelling Application to the ERP: Resource/Agent Maps (RAM)

7.1 Introduction

Chapter 7 includes text and figures from a published journal paper* coauthored with professor Susan Howick and professor Alec Morton (Kazakov et al., 2021), with the exception of figures 7.2.1, 7.2.2, 7.2.3, 7.2.4, 7.2.7, 7.2.8 and 7.3.1 and the text associated with those figures.

Complex Adaptive Systems are systems where agents behave in parallel competing for control over resources in an adaptive manner, subject to a condition/action rule pattern (Holland 1992; Holland 2006). Agents have a predefined goal and are rationally bounded because of incomplete and/or biased information (Fiori 2009; Simon 2000; Simon 1972a). Agents' pattern of behaviour can change in order to adapt to the environment and can involve exchange of information and or resources producing multiplier effects. For example, complex adaptive systems such as healthcare and pharmaceuticals involve multiple subsystems of interconnected agents, resource structures and processes including doctors, patients, drugs and drug suppliers, hospitals and regulators multilevel interrelations that evolve and change together (Roberts 2015; Marshall, Burgos-liz, et al. 2015; Begun et al. 2003) . Financial markets are another example of complex adaptive systems involving suppliers, intermediaries and consumers of financial products in a highly regulated and competitive environment (LeBaron & Tesfatsion 2008; Block et al. 2013).

Gaining a balance in such systems depends critically on resource/agent dialectical interactions. Seemingly small changes at the micro level can lead to a significant systemic misbalance at the macro level, such as in the last global financial crisis (Crotty 2009; Joseph E. 2010; Farmer et al. 2012) or such as the recurrent local and global inefficiencies in healthcare systems related to inequality in access to affordable healthcare and medicinal therapies (Council of the European Union 2016; Haas-Wilson 2001; Plsek 2001). Managing complex adaptive systems can be very challenging, particularly when attempting to control rather than simplify complexity (Rosenhead 2006). One particular problem is the need to take a comprehensive perspective of the complex system in order to manage it effectively (Rosenhead 2006; Ackermann 2012; Ackermann et al. 2014). Problem Structuring Methods (PSMs) have emerged out of the need to help understanding of the behaviour of complex socioeconomic systems and support structuring of key problematic issues (Mingers & Rosenhead 2004; Rosenhead &

Mingers 2001; Rosenhead 2006). An overview of key PSMs can be viewed in Table 7.1.1. A common approach is mapping / modelling system components and their causal interrelations in terms of influence processes, flows, feedback, and emerging properties (Mingers & Rosenhead 2004; Ackermann et al. 2014; Rosenhead 2006).

Table 7.1.1 Overview of key Problem Structuring Methods

PSM	Modelling technique	Theoretical support
Soft Systems Methodology – SSM	Rich picture (Checkland & Scholes 1990; Checkland & Winter 2006;Checkland, 1981; Checkland and Holwell, 1998)	Systems theory (Von Bertalanffy 1968; Forrester 1961)
Strategic Options Development and Analysis – SODA	Cognitive mapping (Eden 1988; Ackermann & Eden 2010; Eden & Ackermann 2001)	Cognition theory (Kelly 1995; Eden & Huff 2009; Foerster 2011; Mingers 1991; Huff 1990; Simon 1955; 1976)
Strategic Choice	Decision graph (Friend & Hickling 2012; Friend 2011; Friend and Hickling, 1987)	Ackoff design approach (Ackoff 1979)
Resource Maps	Resource Mapping (Kunc & Morecroft 2009) (Forrester 1987; M. H. Kunc & Morecroft 2010)	System Dynamics and Systems theory (Forrester 1961; Von Bertalanffy 1968)
Strategic Management of Stakeholders	Stakeholder mapping by Stakeholders influence network and management web (Ackermann & Eden 2011)	Stakeholders theory (Mitchell 1997; Carroll, 1989; Donaldson and Preston, 1995; Freeman, 1984)
Robustness Analysis	Assessing future configurations of the system (Rosenhead 2001; Rosenhead 1980)	Systems theory (Von Bertalanffy 1968)
Drama Theory	Role "hypergame" playing for analysing conflict and cooperation (Bryant, 1997;Howard 1998)	Game Theory (Von Neumann & Morgenstern 1944; Brams 1994)
Decision Conferencing	Analysing decision alternatives (Phillips, 1987; Phillips & Phillips 1993)	Decision theory (Simon 1965), Requisite modelling (Phillips, 1982, 1984)
Viable Systems Model	Cybernetic principles for viable organization (Hilder 1995; Beer 1986; Beer, 1981)	Systems theory (Von Bertalanffy 1968; Von Foerster 1979)

PSMs are inherently dialectic in relation to analysing causal interrelations. However, an important tension in systems theory is between a view of systems in terms of resource feedback structure and in terms of competing agents that adapt and change (Phelan

1999; Hans Jochen Scholl 2001; Mingers & Brocklesby 1997). So far, no PSM has been developed to facilitate the dialectic between these two competing perspectives. In our view comprehensive causal analysis needs to take account for the interconnectedness among resources and agents and bring together both perspectives.

In support of an interdisciplinary approach to PSMs that brings together different perspectives Eden and Ackermann propose that: "Increasingly trans-disciplinary approaches are needed: bringing together social psychology, psychology, mathematics, logic, organization theory (… strategic management), computer science (ICT in visual interactive modelling, to aid facilitation, and provide breadth of modelling options)." (Eden & Ackermann 2006). In addition, Bryson accentuated on the need for "visual mapping for cognitive enhancement and collaborative support techniques" (Bryson et al. 2016). In relation to this and the objectives of my research a need for a visual mapping technique to facilitate the dialectic between the resource-feedback and agent-based views of a system become apparent.

Combining RM with AM to form a hybrid RAM tool brings together the different theoretical and practical resource-feedback and agent-based perspectives. This also supports the view that "… a key role for problem structuring methods is in the nascent and yet growing arena of Mixing Methods" (Mingers, 2006; Ackermann et al., 1997; Howick et al., 2006; Howick and Ackermann, 2011). In order to support theoretically the design of the RAM tool, I have undertaken an enhanced theoretical perspective bringing together RDT (J. Pfeffer & Salancik 1978), RBT (Barney 1991; Wernerfeldt 1984; Peteraf 1993), BDT (Tversky & Kahneman 1974; Kahneman 2003a) and AST (Rosen 1985; Pezzulo 2008). The first two support the Resource mapping tool and the latter two support the Agent mapping tool.

Adding an external resource perspective through the RDT to resource mapping practice (M. Kunc & Morecroft 2010) can enhance problem structuring practice to account for external resource dependence. Agent based qualitative modelling and analysis through Agent Mapping, by capturing agents ''cognitive structure" (Anderson 1999; Macal et al. 2002; Macal & North 2015) can fill a gap in the complex adaptive systems theory and practice of ABM through bringing in BDT and AST. This can aid conceptualization and validation (Heath et al. 2009; Klügl 2008; Kasaie & Kelton 2015) by visualization of agents' cognitive structure in the form of a condition action map, in addition to its methodological use as a problem structuring technique. Further, an integrated RAM can provide a powerful qualitative operational research tool for resource/agent complex system analysis and could therefore be used to support SD/ AB hybrid model conceptualization, model integration (Schieritz 2002; Schieritz et al. 2004; Guerrero et al. 2016b), and validation (Djanatliev et al. 2015) . Complex adaptive system theory can

therefore be enhanced with resource/agent related theories such as RDT, BDT and AST, which in turn will aid the development of problem structuring methods and techniques capable of supporting complex adaptive systems comprehensive and effective management.

7.1.1 Resource Maps

Resource maps (RM) have been used in relation to System dynamics modelling and simulation practice (Kunc and Morecroft, 2005; Kunc & Morecroft 2009; Kunc & Morecroft 2010) to provide a systems approach to the exploration of the concept of "Resource" and "Resource" accumulation and dynamic management (Teece et al. 1997; Teece et al. 2008; Helfat 2011; Helfat & Peteraf 2015; Sirmon et al. 2007). RM is a qualitative mapping technique tightly linked to cognitive mapping (Eden 2004; Bryson et al. 2016; Eden & Ackermann 1992; Ackermann & Eden 2010), employing stock-and-flow and influence diagrams, with the aim of mapping managers' cognitive models focusing on key /strategic resources and resource-building decision making processes (Kunc & Morecroft 2009).

Resource maps have been applied mainly for the representation of systems of firms/agents' asset stocks believed to be key for building competitive advantage and superior business performance and, informed by Resource based Theory (RBT), (Barney 1986; Barney 1991; Wernerfeldt 1984; Peteraf 1993) present an internalized perspective of resource management. However, existing research that uses resource mapping (Kunc and Morecroft, 2005; Kunc & Morecroft 2009; Kunc & Morecroft 2010; Kunc & O'Brien 2017) does not consider the external perspective of resource dependence related to RDT. Extending resource maps through the external perspective taken by RDT (J. Pfeffer & Salancik 1978) can therefore complement and extend the RM theoretical frame and its analytical capacity.

RDT (Jeffrey Pfeffer & Salancik 1978; Hillman et al. 2009) view the organization as being an open system, dependent on contextual contingencies in the external market and regulatory environment. External micro and macro-economic context influence organizational behavior and a key goal of market agents would be reducing environmental uncertainty and dependence on valuable resources through control over vital resources (Ulrich & Barney 1984) by reducing competitors' and institutions power over them, attempting to increase their own power over their competitors. RDT can provide an awareness of the resource dependent forces on organizational behavior and how organizations take actions to manage external interdependencies in order to reduce

uncertainty and dependence on the larger social economic system, including market regulation. In addition, integrating RDT with the resource-based theory of the firm (Barney 1991; Wernerfeldt 1984; Barney 1986) can provide a complementary focus on resources, and may offer new insights into the organizational resource depending behavior, including controlling valuable, rare, nonsubstitutable, and limited resources from the external environment (Hillman et al. 2009) where each agent group interacts and contributes to the overall complexity of the market socio-economic system.

7.1.2 Agent Behaviour Maps (AM)

A limitation of RM is its inability to account for market agents' behavioural decision making due to its theoretical connection to the RBT only having a focus on internal resources. This limitation is confirmed by Phelan (1999) and Schieritz & Milling (2003), who have argued that a stock and flow diagram, i.e. a system's resource structure, is static and focused on the quantity rather than the quality of resource interrelations, and that an agent perspective is needed to enable quality to be modelled. In this case, quality relates to the agents' behaviour in changing the level of a system's resource through flows of action in response to anticipated environmental change. Further, Scholl (2001) and Schieritz & Milling (2003) argue that integrating both a system dynamic and agent-based perspective could provide a means for capturing both the macro and the micro level, and that joint application may deliver superior results.

Agents have a predefined goal and follow a "schema" or a rule/pattern of behavior, which are "mental templates that define how reality is interpreted and what are appropriate response for a given stimuli" (Dooley 1996). They are rationally bounded due to incomplete and/or biased information (Fiori 2009; Simon 2000; Simon 1972a) and could have multitude of rules which are formed through a "selection-enactment-retention process" (Gell-Mann 1997; Holland 1992; Jantsch 1980; Mingers 1991; Maturana 2002; Prigogine & Stengers 1984). Agents' pattern of behaviour can change purposefully or randomly or by combination with other schema in order to adapt to the environment and can involve exchange of information and or resources producing multiplier effects based on the nature of interconnectedness in the system with flows that may be nonlinear.

Two frameworks that can be helpful for thinking about agent mapping are BDT and AST. In terms of BDT research, Simon (1972), Kahneman and Tverzky (1982) and Kahneman (2011) provide a theoretical underpinning for the development of AB mapping technique for complex adaptive systems Market agents, whether they are individual or organizational, which follow certain behavioural patterns informed by their perception of

the environment and decision making and which are rationally bounded due to incomplete information and imperfect cognition (Stanovich & West 2000; Kahneman & Tversky 1982; Kahneman, 2011). For that reason, agents behave according to heuristic principles in order to reduce judgment and choice complexity (Tversky and Kahneman, 1974; Kahneman & Tversky 1982). These principles include "availability", "anchoring and adjustment", "representativeness" and "loss aversion" (Kahneman and Tversky, 1972; Kahneman and Tversky, 1979). Heuristics can also lead to cognitive biases (Kahneman, 2003) and decision making is simplified through a "Recognition" heuristic which makes best use of the limited information available to individuals (Gigerenzer & Goldstein 2011; Gigerenzer 2000).

A second framework that can be useful for thinking about agent mapping is AST. AST posits that "anticipation is the process which enables a living system to contain a predictive model of itself and its environment, which allows it to adapt by changing its state in accordance with the model's predictions" (Louie 2010; Rosen 1978; Rosen 1985; Pezzulo, 2008) and to base its course of actions on their anticipated effects. Anticipatory systems have the ability to exhibit "payoff" anticipations and "state" anticipations (Butz et al. 2008). Payoff anticipations are pertinent to systems that "have knowledge of behaviourally-dependent payoff and can base action selection on that representation, i.e. "different payoff may be predicted for alternative actions, which allows the selection of the current best action." State anticipation is based on anticipatory processes which enhance behavioural decision making by future anticipatory representations of not only the goal but of the whole system. The next section will describe a Resource/agent map that has been designed to provide qualitative mapping and analysis of resource/agent behaviour.

7.1.3 Developing a tool for comprehensive qualitative appreciation of resource/agent behaviour: Resource Agent Map (RAM)

I have designed an approach to AM, enhanced RM and integrated RAM after two key principles regarding the future of problem structuring practice (Ackermann et al. 2014). These are: 1) borrowing and developing theory and 2) developing effective procedure for mixing methods (Ackermann et al. 2014). In parallel I have taken into account other principles such as building on prior research, creating a potential for generalizable findings and effective collaborative support.

Development of the RAM included the following steps:

- Firstly, a RM enhanced by RDT is developed which maps key internal and external resources, their structure, influencing factors and feedback interrelations;
- Secondly, an AM is developed, containing both an AiM, which maps key agents, their interrelations, influencing factors and identifying the agents' main behavioural rules; and AbM, which maps agents' behavioural decision/action pattern in more detail than the AiM revealing each agent's cognitive structure informed by BDT and AST;
- Finally, the enhanced RM and AM are integrated to produce a hybrid RAM;

In Table 7.1.3 each of the above steps is elaborated in relation to their purpose and theoretical support.

Table 7.1.3 Theory and design purpose behind enhanced RM, AiM, AbM and RAM

Mapping technique	Design purpose	Theory
I. Enhanced Resource Map (RM)	Extends the RM approach (Kunc & Morecroft 2009) based on RBT of the firm, enhanced by the RDT Mapping key internal and external market resources, influencing factors and variables and eliciting feedback interrelations Analysis of resource structure and feedback dynamic	RBT (Barney 1991; Wernerfeldt 1984; Peteraf 1993) RDT (Jeffrey Pfeffer & Salancik 1978; Hillman et al. 2009)
II. Agent Interaction Map (AiM)	Mapping agent interactions building upon the Stakeholders Management mapping concept (Ackermann & Eden 2011) and feedback including identifying each agent's key behavioural decision rules and key influencing factors Analysis of agents' structure and influencing dynamics	BDT (Kahneman 2003b; Kahneman 2003a; Kahneman & Tversky 1982; Gigerenzer 2000; Kahneman & Tversky 1979)
III. Agent Behaviour Map (AbM)	Mapping each agent's behavioural decision rule in more detail through an agent behavioural matrix Analysis of agent decision rules and behaviour	BDT (Kahneman 2003a; Kahneman & Tversky 1982) AST (Louie 2010; Pezzulo 2008; Rosen 1985)
IV. Resource Agent Map (RAM)	Integrating Enhanced RM and AM into a hybrid RAM Analysis of resource/agent interactive behaviour and identification of scenarios emerging out of variations in resource and structure, agent behavioural rules and contextual factors	Integrating Systems with Complex Adaptive Systems theories (Phelan 1999; Schieritz & Milling 2003; Guerrero et al. 2016; Borshchev & Filippov 2004)

Pharmaceutical and health care systems are appropriate systems for application of RAM as they are complex adaptive systems (Roberts 2015; Marshall, Burgos-Liz, et al. 2015; Marshall, Burgos-liz, et al. 2015; Begun et al. 2003; Djanatliev et al. 2015; D.Roberts 2011; Macal & North 2015) from which dynamics emerge out of the interactions among competing agents and resource structures. Both the resources, agents and their relationships change over time maintaining "complex systems of changing problems that interact with each other ..." (Ackoff 1979). Our aim is to show how RAM can help decision makers achieve comprehensive evaluation of the effect of complex health care interventions such as pricing regulation in EU, including generating management scenarios for optimal system regulation.

7.2 Application of enhanced RM in the ERP project

In general, the market resources (medicine, public budget, etc.) provide the carrying capacity of a market system. Their stock levels can evolve through accumulation and depletion (by resources inflows and resources outflows) which are influenced by market agents´ interactive behaviour, other resources and endogenous systemic factors, including information feedback effects. Key resources identified on the given RM are provided in Table 6.1.B in Chapter 6. Boxes are stocks of resources, inflow and outflow arrows with converters denote rates of accumulation and depletion of resource levels. Circles are endogenous factors/variables influencing resource levels. All Interrelations between resources and influencing factors are marked by connection arrows, denoting the direction of influence. All endogenous systemic factors included in the RM can influence the level of market resources either positively or negatively, depending on their dynamic properties. The influencing factors include market agents' activity, market regulation, product price and information availability. The modelling graphical language is borrowed from the system dynamics practice and software.

A version or an enhanced RM is given on Figure 7.2.5, which provides a qualitative model of the ERP system conceptualized through SD (Morecroft 1999; Kunc & Morecroft 2009; Kunc & O'Brien 2017), RBT (Barney 1991; Peteraf 1993; Wernerfeldt 1984; M. Kunc & Morecroft 2010) and RDT (J. Pfeffer & Salancik 1978; Hillman et al. 2009) perspectives and built from the collected information discussed in the previous section. Building the enhanced RM required elicitation of key feedback loops responsible for the endogenous dynamics of the ERP system, explained in the following pages. This involved mapping the main resources and resource flows identified through the data collected and described in Table 6.1.B and Table 6.1.C.

The mapping procedure included iterative steps between statements in the documented data describing main ERP system resources and key influencing factors, the interrelations between influencing factors, resource flows and resource levels using arrows to denote the direction of influence or interdependence.

The design of enhanced RM, AM and RAM included the following main stages:

A. Enhanced RM design

I. A Causal Map (CaM) of main statements on ERP effects, eliciting main causal structures in the system (interpreting the statements about the effects of ERP regulation), following Kim and Anderson (2012) and Turner, Kim and Anderson (2014) use of the term 'causal maps' in a broader and general sense, meaning maps containing causal structures.

II. Macro level CaM in the form of a Causal Loop Diagram (CLD): global perspective (internationally)

III. Micro level CaM in the form of a CLD: local perspective(one country)

IV. Mapping of "resources" concept over the Micro CLD from the perspective of resource maps method (Kunc and Morecroft, 2010)

V. Enhanced RM design in software

B. AiM and AbM design

VI. CaM of main statements (going back and redesigned) to reflect market actors' decisions and activities

VII. AiM and AbM drafts for interrelations and rules

C. RAM design

VIII. RAM draft: new CaM on which to position resources and agents in a combined (interrelated) perspective

IX. RAM in software iterative versions including that version from published journal paper (Kazakov et al., 2021)

Figure 7.2.1 provides main coded statements, taken from documented sources related to the ERP effects on the market system, grouped on a causal map. The procedure of eliciting causal structures from a purposeful text followed Kim and Anderson (2012), and Turner, Kim and Anderson (2014) paper, which demonstrated the design of causal maps from the Federal Open Market Committee meetings and assertions, which later supported

the design of causal loop diagrams with the purpose of crafting and validating formal simulation models.

Also, the term 'causal maps' and 'causal mapping' are used here to denote different methods for eliciting word-and-arrow diagrams directly from qualitative data (Axelrod (1976) or Eden et al. (1992), with the purpose to derive structural relationships among a set of causal assertions or statements made by a stakeholder or stakeholders group. Each concept or statement is represented by a word or a phrase, and the relationships between concepts or statements are specified with an arrow (with or without specifying positive or negative polarity to show the nature of the causal relationship). Arrows between statements can represent not only causal connections but they can denote a sequence of events or other forms of influence (Kim and Anderson, 2012).

Statements labelled with the number 1 come from the EC commissioned DE simulation project (Toumi et al. 2014) on ERP regulation regarding drug price spillover effect, incentives for pharmaceutical companies to engage into product launch sequence activities and regarding limitations including need to account for parallel trading of drugs among EU countries and other drug pricing policies interfering with ERP.

Statements labelled with the number 2 come from innovative and generic industry associations: "ERP interferes with other price lowering tools and can lead to lack of available, affordable drugs either generic or innovative".

Statement with the number 3 provide evidence for strategic pricing and state price discounts (Vogler et. al. 2015).

Statements labelled with the number 4 provide information on industry retaliation activities in response to the ERP regulation, like (Carone et al., 2014, Vogler et al., 2015, Toumi et al., 2014):

- pharmaceutical companies give non disclosed discounts to distributors
- drug launch prioritisation
- compete on price discounts
- keep prices higher to exploit ERP

Statement number 5. comes from Kanavos et. al. (2010) giving info on launch delays and product withdrawals used among market actors .

That procedure produced drafting and redrafting subsequent causal maps which supported the purposive design of a representative RM containing all components characteristic for the RM technique. Figures 7.2.1, 7.2.2, 7.2.3 and 7.2.4 present the maps drafted in support of the enhanced RM design. Redrafting of the maps followed the

iterative steps of the maps creation through the authors continuous reflection on the maps correct representation of the ERP market system, coming out of the documented statements of the stakeholders about the ERP systems' resources, actors and their interrelations.

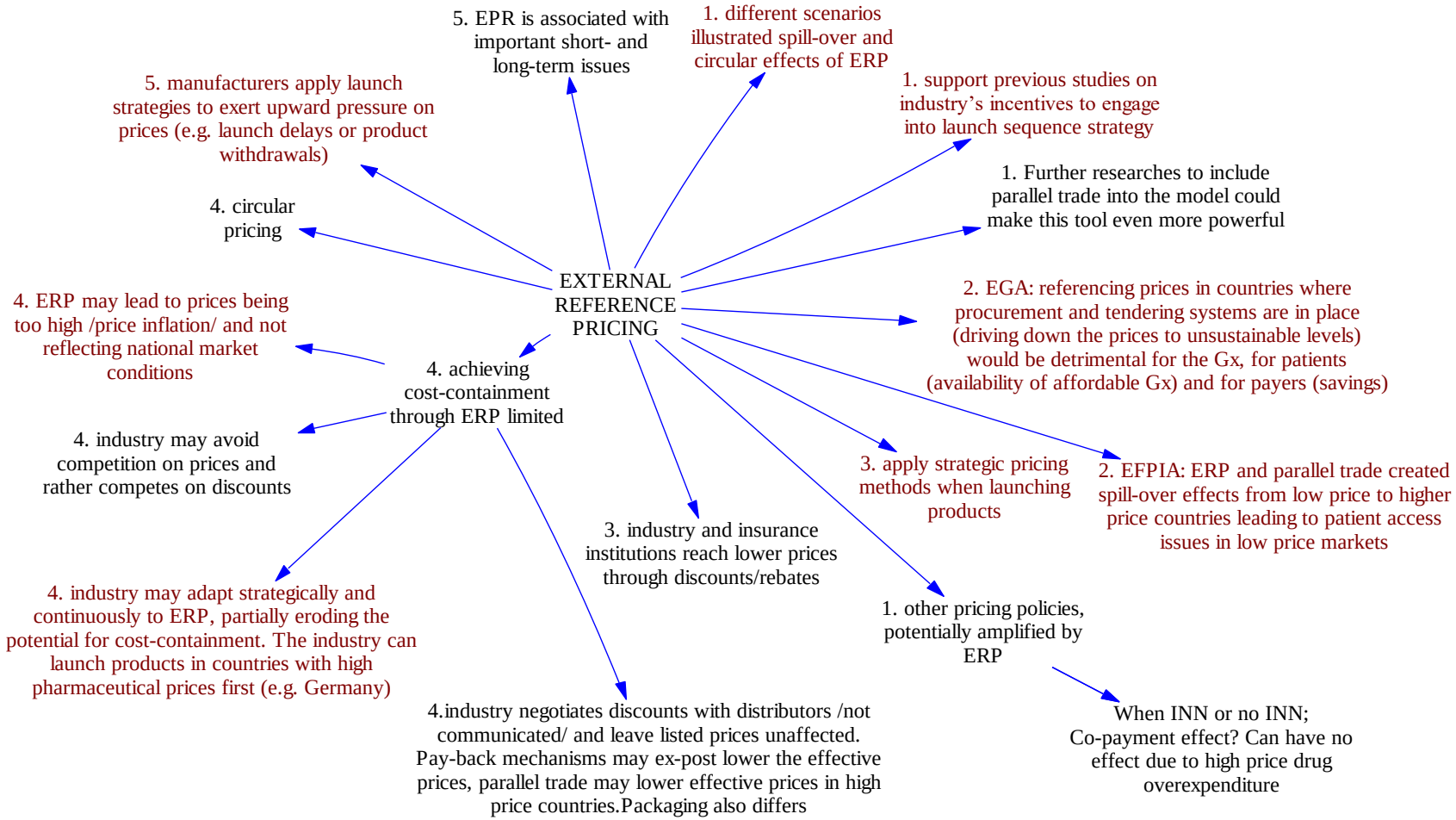


Figure 7.2.1 Main coded statements taken from documented sources related to the ERP effects on the market system

Initially a macro level CaM of product pricing (Wolstenholme 1999; Howick et al. 2008; Howick & Eden 2009; Diaz et al. 2015; Coyle 2000; Kazakov & Petrova 2015) was constructed in the form of a CLD following main documented statements presented in previous Figure 7.2.1, regarding resource, agent and their interaction components of the pharmaceutical market. The goal of that map is to frame the system boundary and factors influencing drug pricing, like competition and information imperfection, and to support the design of the extended RM. A macro level like CLD related to the public drug price approval regulation has the goal of also depicting the contextual effect of External Reference Pricing (ERP), Internal Reference Pricing (competition on INN), and Parallel Trade (PT) on product market and product price

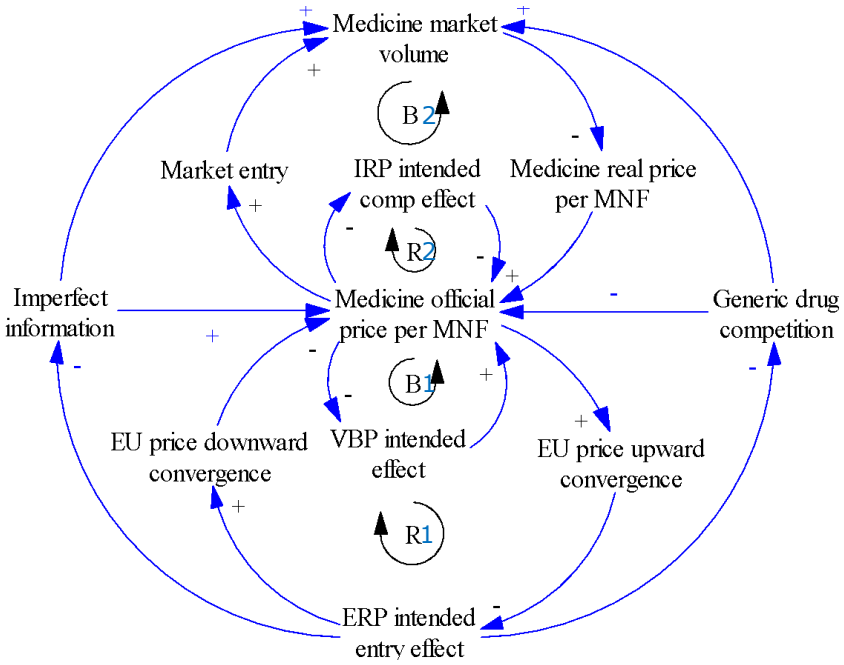


Figure 7.2.2 A macro level CLD related to the public drug price approval regulation and contextual effects

Key insights which we can get from Figure 7.2.2 would be related to the effect of the external reference pricing (ERP), which could lead to the counterintuitive EU wide upward price convergence or maintenance of a higher price for a longer period of time ('EU price upward convergence' in Loop R1 on the CLD informed through statements with labels 3, 4 and 5 from the previous Figure 7.2.1, which also inform 'Market entry' and 'Imperfect competition'). Another one could be that ERP alone (without other pricing regulation directed to product competition) would not produce the intended effect of lowering product price (''Medicinal real price per MNF' and Medicinal official price per MNF' in Loop B2, informed through statements labeled with number 4).

'EU price downward convergence' in Loop R1 on the map was informed through the innovative and generic drug industries statements labeled 1, 2 and 3., which also inform 'Medicine market volume' and 'Generic drug competition'.

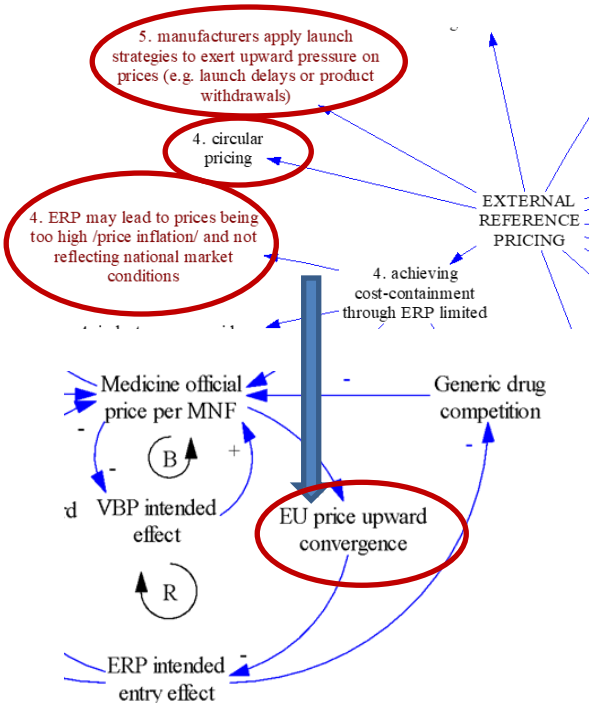


Figure 7.2.2.a How statements from Figure 7.2.1 inform variables in Figure 7.2.2

Figure 7.2.2.a gives an example of how statements 4 and 5 from Figure 7.2.1 are transformed in one variable 'EU price upward convergence on Figure 7.2.2. In addition, a micro level CLD on Figure 7.2.3 was made in a next iteration stage to transform the macro CLD components into a local market micro CLD, which to take account of and exhibits feedback relations among demand from patients and supply from drug manufacturers, constrained by budget resources, public and market retail price, contextual price regulation and market competition. That micro level CLD followed the logic of interrelations within the macro CLD and had the goal to capture local market functional interrelations and effects connected to the ERP effect on the market. 'Medicine market volume' transformed into 'Country supply' and 'Country demand' linking them to 'Official medicine price for reimb', 'Agreed with payor % off public price', 'Retail price', 'Public Pharmaceutical Budget' and 'Competition' including local contextual price regulation factors like 'INN prescribing' etc. and 'Parallel Trade'. Connections to the documented statements included in the CoM are evident and can be followed back to all of them, through the previous explanation of Figure 7.2.2. A number of important interconnections and feedback loops have emerged on the micro CLD, like 'Parallel Trade' and 'Country supply' and official public price, price discounting and retail price, competition and retail price and prices and 'Country demand'. All these interrelations

between factors, resources and market actors' activities are affected through the ERP regulation. Inadequate price regulation and inappropriate level of public funding would have negative effect on demand which in turn would keep the product price higher if not enough condition for market competition.

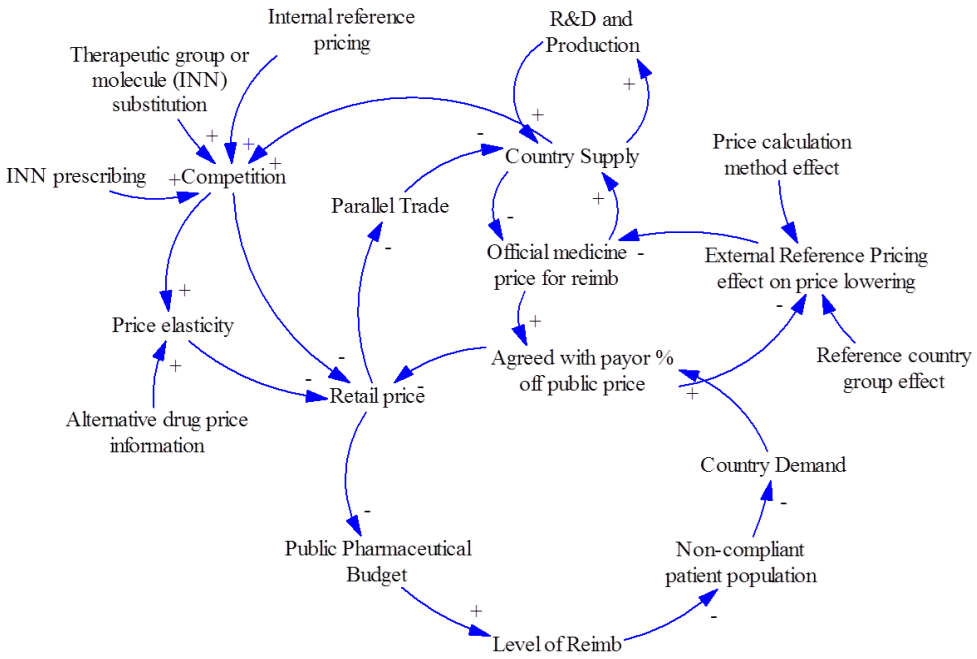


Figure 7.2.3 A micro level CLD of the ERP effect on the pharmaceutical market

Reflecting on the micro level CLD of the ERP regulation effects on the market system, further a next iteration of the map was created, containing drafted layer over the map from the perspective of the resource maps method (Kunc and Morecroft, 2010), containing main resources conceptualization and in addition including actor's conceptualization within the market system (Figure 7.2.4). For example, 'Country supply' and Country demand' factors were conceptualized as connected to drug stock resources and labelled with 'R' and a rectangular shape with incoming and outgoing flows notation. Other factors on the map which were conceptualized as resources were official drug price and retail price, parallel trade and drug public budget. The main criterion for a resource was that resources or stocks of resources can increase, accumulate or decrease, following from main system dynamics concepts regarding stocks and flows and their graphical notation. What was interesting, doctors and patients connected to the drug resources demand factor, were conceptualized both as resources 'R' and agents 'A'. On one side, they are strategic resources for the government and the drug companies, but on the other side they can take decisions and actions related to prescribing or buying a

drug, this influencing on drug stock resources in a local market. Other important market agents are the government (pricing authorities) and pharmaceutical companies (drug manufacturers and drug parallel traders), which have influence with their decisions on the ERP rules and on drug resources supplied to a local market or traded among EU countries.

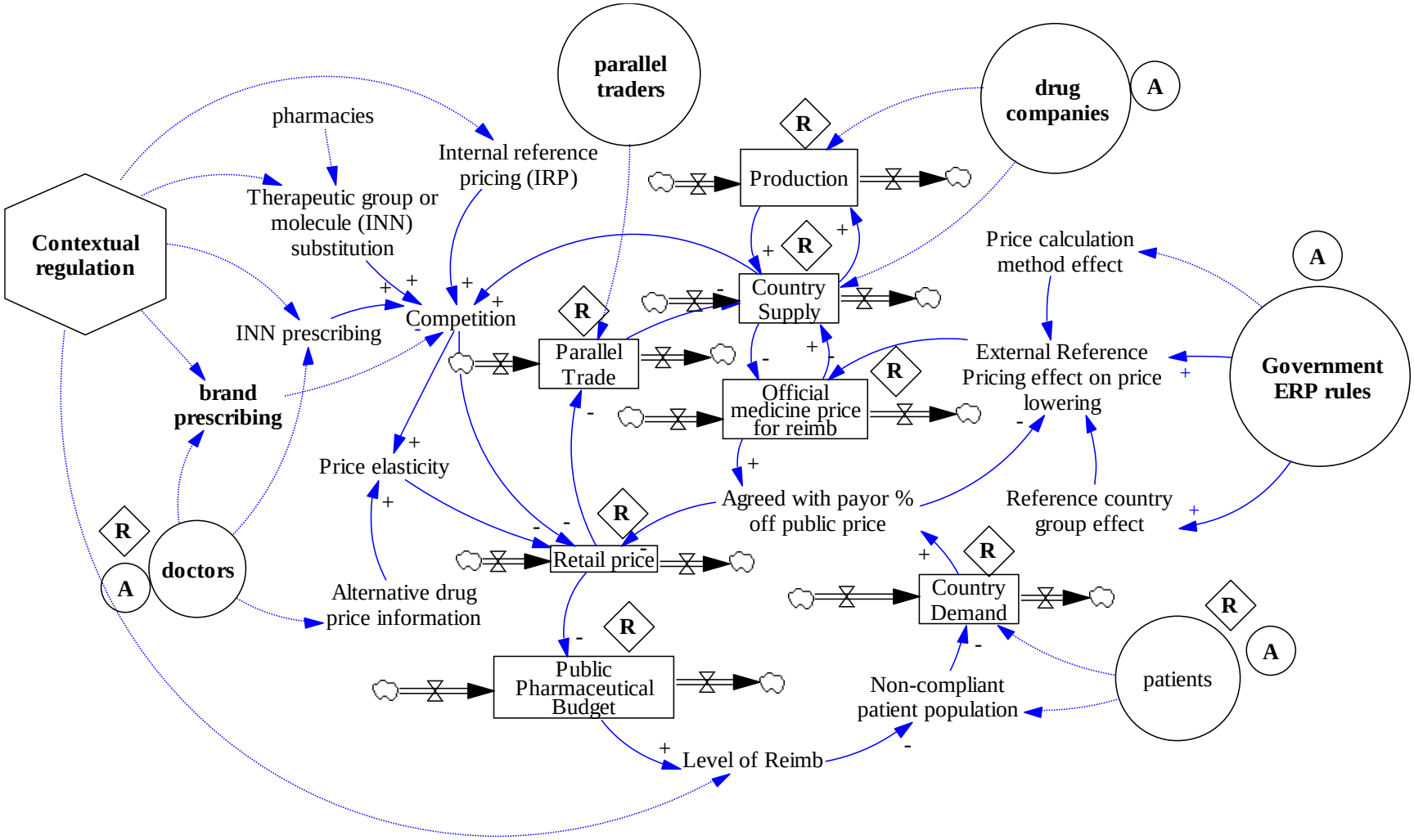


Figure 7.2.4 Reflecting on the micro level CLD of the ERP regulation effects on the market system, bringing resource and agent perspectives

In that respect and line of working a next version of the micro CLD emerged this time following the conceptualization of a resource mapping method (Kunc and Morecroft, 2010), reflecting on the market system resources from internal and external perspectives (explained in the theoretical framework), connected to the RBT and RDT. Figure 7.2.5 provides this RM version on which 'Drug supply' and 'Country demand' factors from the second drafted version of the micro CLD were transferred into 'drugVolumeSupplied' and 'drugVolumeBought' on the enhanced RM. 'Parallel Trade' was transformed into 'ParallelExport', Public Pharmaceutical Budget' became 'DrugPublicExpenditure'. 'Official medicine price for reimb' was transferred in 'DrugPublicPrice' and 'Retail price' became 'DrugMarketPrice'. 'External Reference Pricing effect on price lowering' was relabeled to 'ExtReferPrice' and 'ERPEffect'.

Doctors and patients were included as resources on which competition ('DrugCompetitionEffect') has effect to prescribe or buy drugs. 'DecisionSupply' was included to denote important point of drugs entering into a local market, reflecting drug companies' decisions when to supply drug to a chosen local country market. 'Agreed with payer % off public price' was included in the enhanced RM as 'PayerPriceDiscount'.

During the process of working and reflecting on the maps and their iterative versions and transferring them into an enhanced RM, and thinking on the resource conceptualization of the ERP effects on the drug market system, the notion of main market agents' decisions that are influencing on resource levels, started to emerge. That was later developed in the process of drafting agent maps and when combining the enhanced RM with them into a hybrid RAM. Also, that notion was applied further in the software specification of the hybrid SD and AB simulation interactions between agent decisions and resource levels, through their influencing on stocks inflow and outflow rates.

When the map was completed, the pharmaceutical ERP system structure was differentiated by three different coloured interconnected substructures: Innovative drug market, Market with generic drug competition, and Parallel trade market. They emerged to have a separate and combined influence on the ERP system in relation to resource levels and agents' behaviour.

The next phase of the mapping process included identification of important reinforcing (R) and balancing (B) feedback loops, which provided the nonlinear dynamic state of the pharmaceutical market system. These loops were highlighted by examination of the interconnections between the system resources. A key variable in the market is product price (the officially approved price and the one used in the retail market). The higher the officially approved price of a medicine (drug molecule) in a price reference country, the higher the product public price in the referenced country (Loop R1), and the higher the

capability for supply (volume) of that molecule (either under patent or off-patent), evident in Loop R2. However, this reinforcing feedback loop could produce the opposite cycle if the referenced and then the reference price start to decrease.

The higher the effect of the ERP in one country on price lowering, the lower the level of the official drug price. In turn, there would be a lower willingness to supply the drug in certain countries for economic reasons and to evade circular price benchmarking among ERP countries. Maintaining a higher market price per manufacturer would result in a higher profit margin, which would increase manufacturing and supply. This in turn would allow companies to relax the retail price in a monopolistic patent market, giving larger discount to the public payers (Loop B1); in addition a higher market price would decrease drug consumption in an off patent market which would produce competitive pressure on price discounting, leading to a decrease in market price (Loop B2). Another important factor on the market, will be the level of the parallel trade (buying the imported medicine from a lower priced national market and re-exporting it to an EU country with a higher priced molecule). This would affect the local market drug volume negatively through reduced drug availability and a decision not to supply to that local market (Loop B3).

However, market competition (supply of the molecule by rival companies) could offset the availability problem, either without or with a delay. The degree of market competition would be higher with the higher number of suppliers (generic medicine manufacturers) entering the off patent market, and would be generating higher demand through an increase in incentivizing activity and doctor prescriptions (Loop R3).

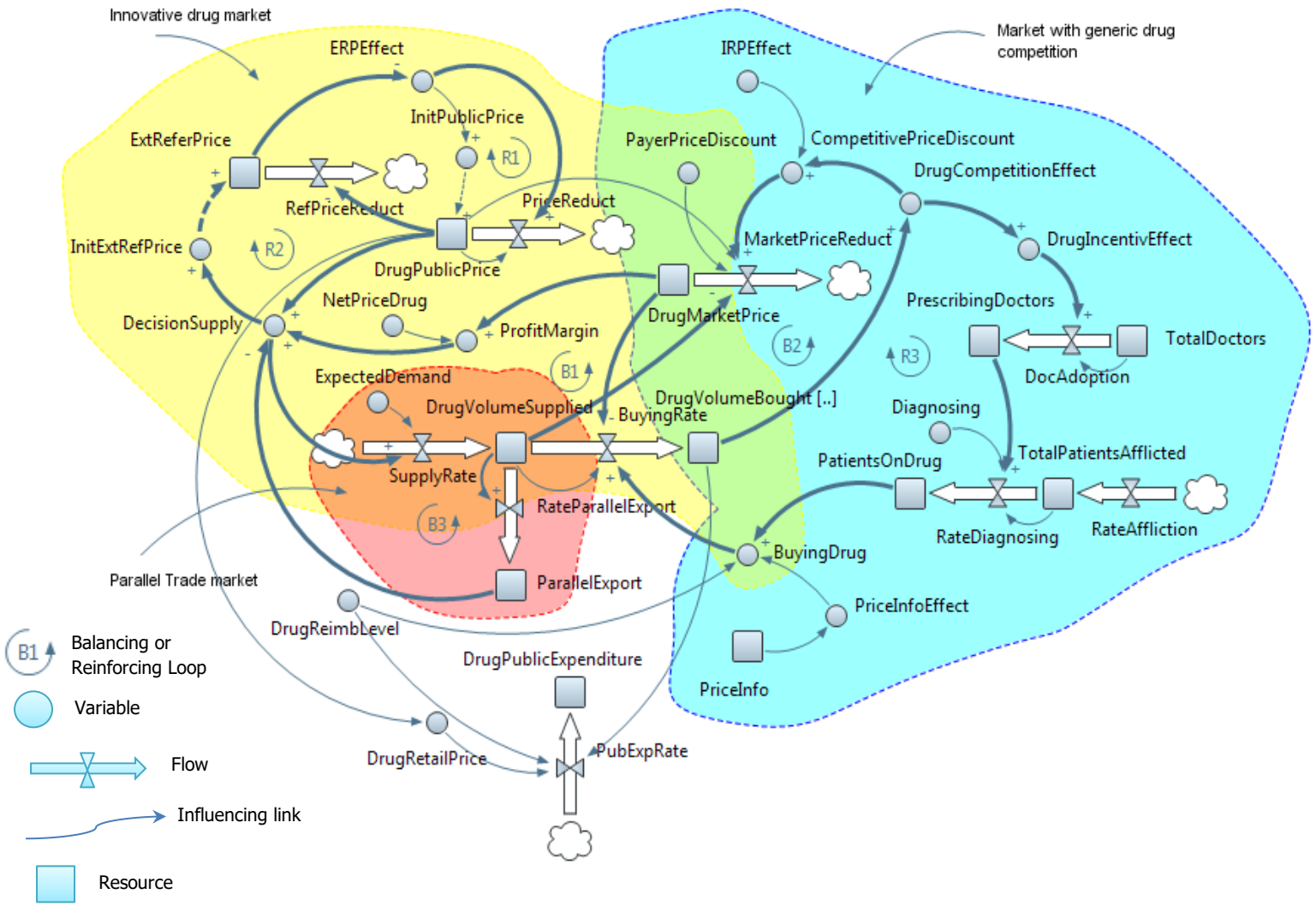


Figure 7.2.5 Enhanced Resource Map of the ERP regulation system

An AiM of the pharmaceutical market is provided on Figure 7.2.6. The key market agents influence each other's behaviour by interacting with each other within the constraints of the market environment/regulation. Manufacturers are influenced by Pricing and Reimbursement, and Prescribing and Dispensing regulation, including drug public price, controlled by the government's expenditure budget. Doctors and Pharmacists are influenced by companies and government incentives. Patients are influenced by Doctors and Pharmacists and by the level of information they have regarding medicines price. The Agent interaction map on Figure 7.2.6 describes the drug manufacturing (MNF) agent as following three main condition/action rules: Agent Supply Rule, Market Pricing Rule and Doctor Incentivizing Rule, the first two of which are analysed in more detail by the Agent behaviour map in Figure 7.2.9.

The Agent Supply Rule, i.e. manufacturing agent supply condition/action routine is affected not only by the ERP rule controlling the public price of the medicines, but also by a number of market factors such as the limited allocated public drug budget for which company agents compete, drug demand, market price competition and drug actual price. Prescribing regulation influences doctors prescribing patterns and doctor incentivizing rules, which in turn influence doctors prescribing rule by brand incentivizing activity; dispensing regulation influences pharmacy dispensing rules and drug agent market pricing rules, which in turn influence further dispensing patterns by product price discounting; reimbursement regulation influences market pricing rules through drug market price competition and patient buying rules through the level of reimbursement and patient co-payment.

The agent interaction map reveals not only who influences who, but which agent behavioural rule influences other rules. The ERP rule effect on drug manufacturing agent behaviour is imposed directly on agent decisions to supply through drug public price setting and indirectly on agent market pricing rules through the market price discount. Furthermore, a pharmaceutical firm agent supply and market pricing rules are influenced by key market factors like drug demand, drug public budget appropriation, market price competition and parallel export/import. Market Agents, individual or organizational, follow a behavioural pattern, determining what action they take at any time and after what rule, informed by their perception of the environment and optimal decision making. Agents can change their behavioural pattern prospectively or reactively in order to adapt to the changing environment.

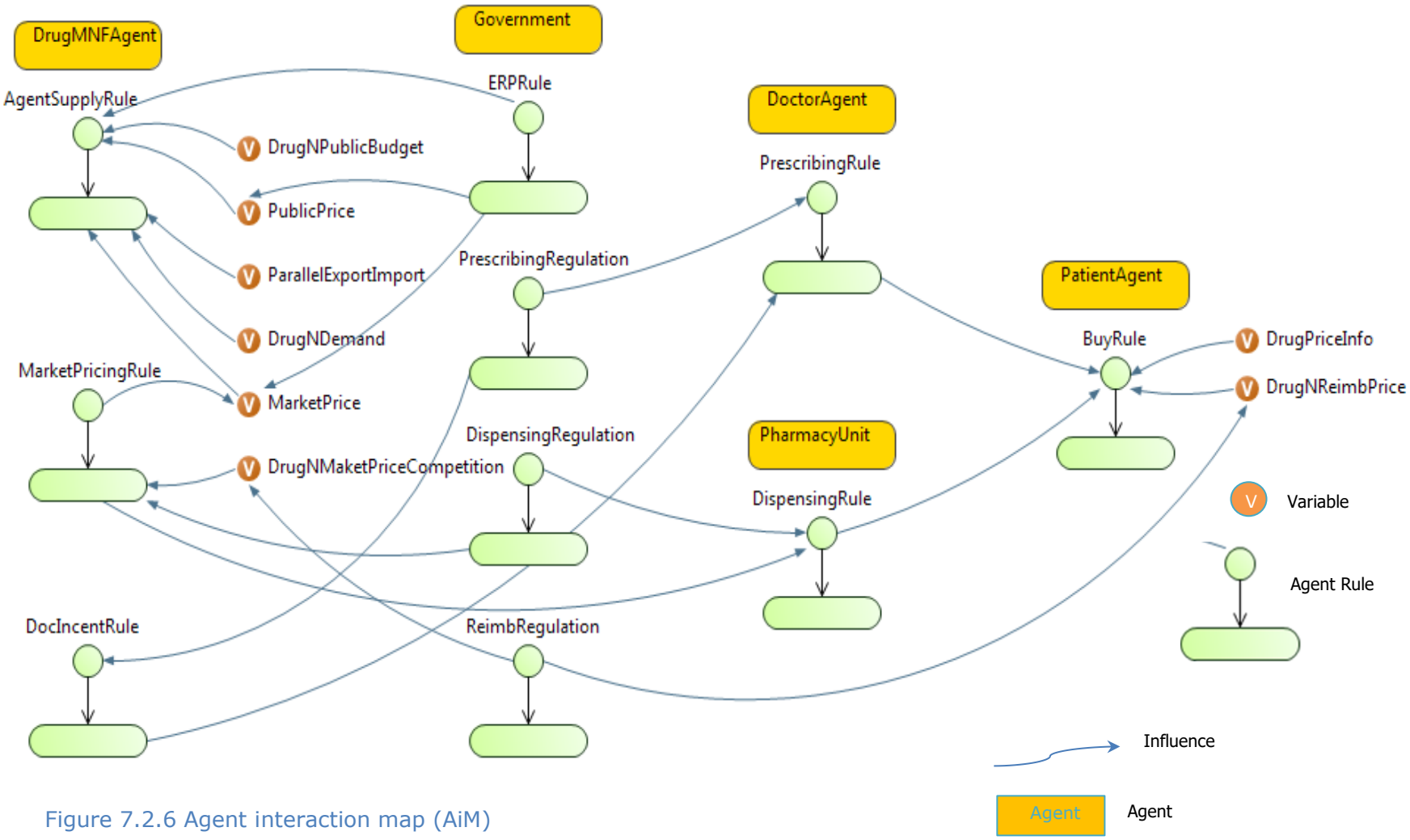


Figure 7.2.6 Agent interaction map (AiM)

Main agents (market actors) on the ERP market system were identified from the documented assertions and working through the process of drafting and redrafting CoM, CaM and enhanced RM, including conceptualization of agents' main behavioural rules in respect to the ERP effect on the market.

Each agent was positioned on the map in order from left to right, from drug manufacturer to government, doctor, pharmacist, patient, with corresponding labels for main behavioural rules of each actor. 'DrugMNFAgent' do mainly drug supply, drug price formation and drug marketing, so their rules were labelled: 'AgentSupplyRule', 'MarketPricingRule' and 'DocIncentRule' (rule for drug marketing incentivizing doctors to prescribe a drug). Government agent makes decisions regarding the ERP tool set and other contextual drug pricing regulation, so 'GovernmentAgent' rules were labelled 'ERPRule', 'PrescribingRegulation', 'DispensingRegulation' and 'ReimbRegulation'. Doctors prescribing decision rules are labelled 'PrescribingRule', pharmacists have 'DispensingRule' and patients buy medicines having 'BuyingRule', although there are other decisions and decision rules, the AiM includes main behaviors and associated rules which are relevant to the ERP effect research question.

Also, important influencing factors (taken from the documented statements) were included among agents and their rules (drug budget, public price, parallel trade, drug market price and drug demand, price competition). Interconnections between each agent rules and important factors have been made in order to correspond to main documented statements and assertions.

The Agent-behaviour routines emerged from the collected information and the agent interaction map analysis, and depicts the drug manufacturer forward looking behavioural model. This relates to the market agent's performance goals and to the agent's organization's future economic state. It is presented in Figure 7.2.9 as a matrix of interlinked anticipated goals, heuristics, and conditions/actions.

The main documented assertions regarding the market agent behavioural patterns and conditional components of the AiM were initially worked out through drafting and redrafting on previous maps (Figures 7.2.1 and 7.2.4) , resulting in a redrafted CaM (Figure 7.2.7) with reconnected components to reflect better how the ERP regulation incentivize the main market agents' decisions and actions in the perspective of a condition to action sequential causal structure of interconnected statements about their behavioural pattern (Figure 7.2.7 and 7.2.8). That procedure followed a reflection on the previous maps and on the principles for agent behavioural rules described and supported through CAS, BDT and AST combined theoretical framework.

The initial CaM as redesigned from Figure 7.2.1 with the purpose to highlight the condition to action agent behavioural pattern (Figure 7.2.7), regarding the manufacturer's decision rules to supply drugs and to manage drug pricing, conditioned on the ERP regulation and market logic. Comparing Figure 7.2.7 and Figure 7.2.8, one could follow which documented statement regarding the ERP effects on the market system and main actors behaviour informs agents condition and action rules pattern (connected to drug MNF agent): statements 1a, 1b, 4d, 3b and 5b inform drug MNF agent 'Action 1' and 'Condition 1', 'Action 2' and 'Condition 2', statement 3a informs 'Action 3' and 'Condition 3', statement 4a and statement 4b inform 'Action 4' and 'Condition 4', statement 4c informs 'Action 5 ' and 'Condition 5', while 'Action 6' comes from common market logic, regarding drug market competition effect and refers back to the generic drug industry official statements (Toumi et al., 2014). Statement 5 informs 'Action 7' and 'Condition 7', while statement 4d informs also 'Action 8'.

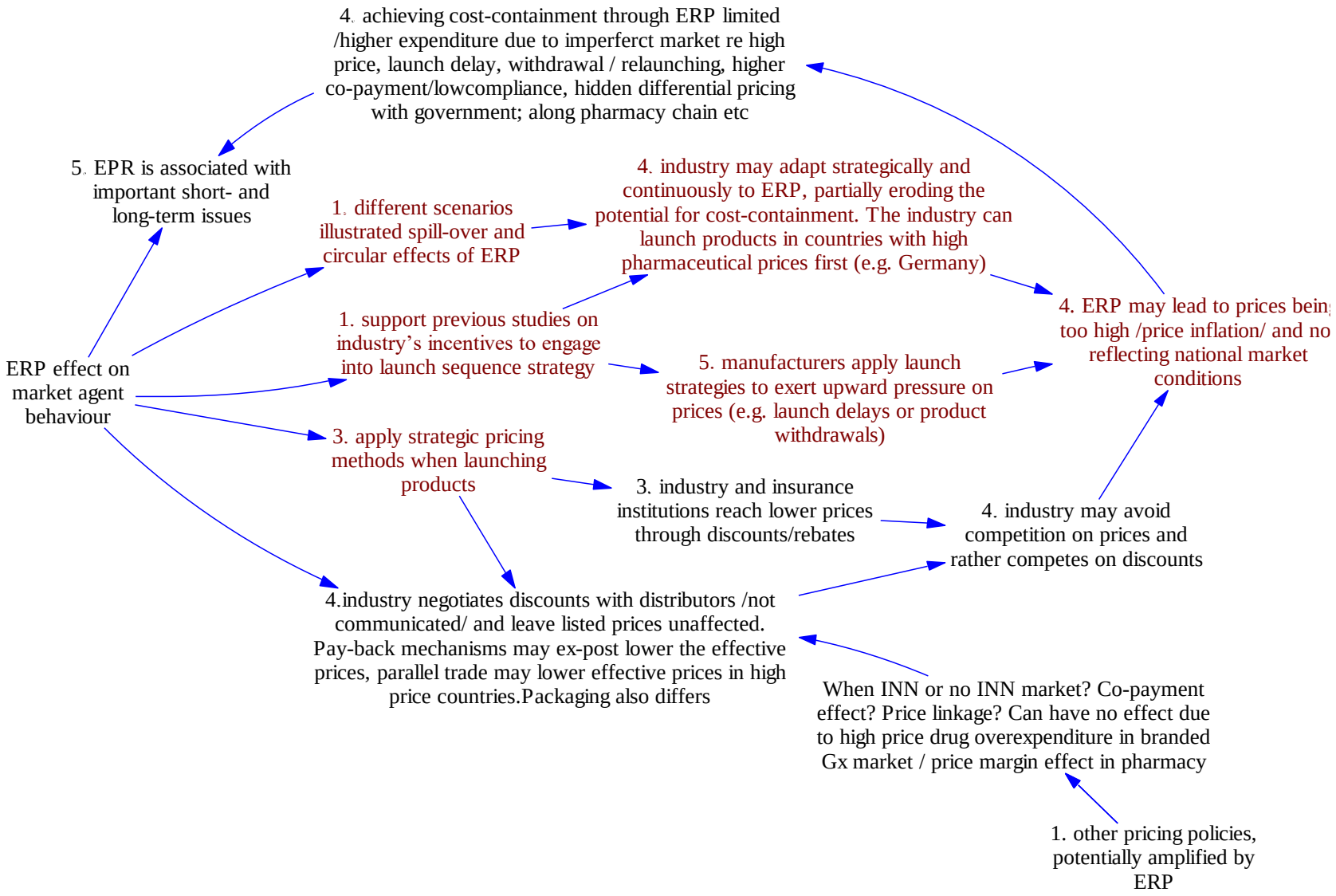


Figure 7.2.7 Initial agent behaviour map, drafted after documented statements

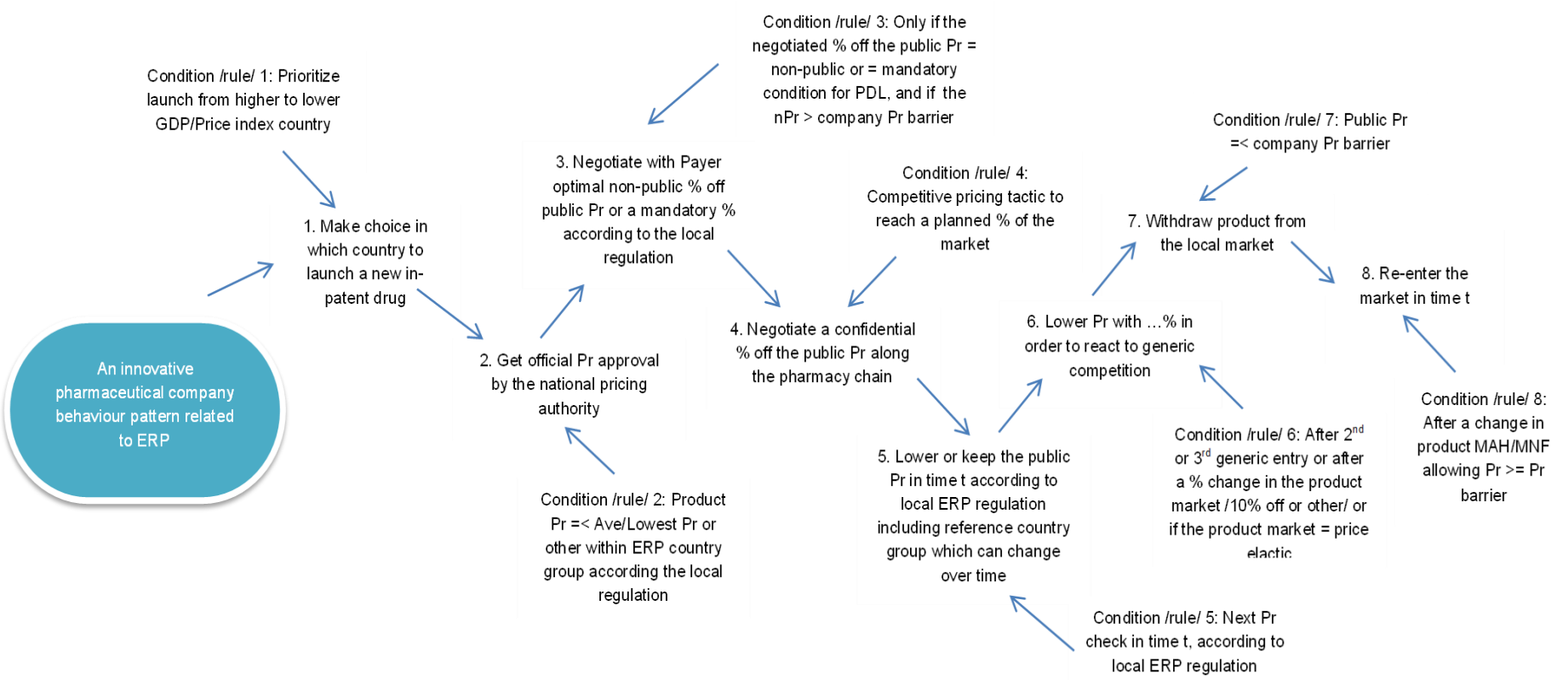


Figure 7.2.8 Version II of agent behaviour map draft including conditions associated with actions

On the next drafting step, a next version of the AbM was designed in software, reflecting further on connections between agents' sequence of activities and their relevant rules from the AiM, denoting arrows representing actions with label 'A' and arrows representing conditions with label 'C'. Also, an overarching goal (reflecting AST) and main guiding decision heuristics principles were included in order to denote agents' goal anticipated behaviour and behavioural decision making guiding scheme.

The AbM on Figure 7.2.9 depicts each decision/action routine for a chosen agent based on the agent interaction map and on the previous agent behaviour maps versions (Figures 7.2.7 and 7.2.8). The depiction of agent behaviour, i.e. decision/action routine was informed by the collected data regarding stakeholder assertions on the ERP effect and related pharmaceutical companies response, depicted on the previous agent map versions, but this time following a BDT (Kahneman & Tversky 1979; Kahneman 2003a) and AST (Rosen 1985; Pezzulo 2008; Butz et al. 2007) framework protocol. Figure 7.2.9 represents a network matrix of agent condition/actions sequence based on agent anticipated action related goals, guided by the agent's main behavioural heuristic and decision system. The mapping starts from the top of the matrix using short phrases linked by unidirectional arrows that provide description of the agent's anticipated goal, the agent decision heuristic, the agent's actions and related conditions for each action, using arrows labelled "A" for action and "C" for condition. On the right side of the matrix the decision/action routine is aligned to the goal, heuristic, condition/action and decision system protocol, while on the left side agent behaviour rules are mapped.

The drug manufacturing AbM in Figure 7.2.9 provides insight about the behavioural routine of the pharmaceutical agents in response to the ERP regulation in EU. Drug Manufacturing Agents have an anticipated payoff (Butz & Pezzulo 2008; Pezzulo & Castelfranchi 2009) or economic return on investment in R&D attached to any product launch, in the form of a planned profit margin percentage ratio, with a minimum barrier which should not be overpassed. Their price decision making is driven by the dominant logic of the market (Prahalad & Bettis 1986; Helfat & Peteraf 2015), following anchor and adjustment and loss aversion behavioural heuristics (Kahneman & Tversky 1979; Stanovich et al. 2010; Kahneman & Tversky 1982; Kahneman 2003b; Kahneman 2003a; Tversky & Kahneman 1974; Schwenk 1984; Schwenk 1988; Simon 2000; Simon & Feldman 1959; Axelrod 1976).

The anchor and adjustment principle related behaviour is translated into a sequential product launching activity in the EU country markets, "anchoring" the local price in high GDP countries which can support higher price setting than other countries; and then "adjusting" the public and market price through mandatory or nondisclosed price negotiation with local payers, and further through competitive discounting (Carone et al.

2014; Leopold et al. 2012; Vogler & Paterson 2017; Vogler et al. 2014; Schneider 2017). Further, the above price setting heuristic allows pricing the product at an optimal level and exploiting an upward feedback pricing effect through the ERP regulation.

The loss aversion principle behaviour is translated into 'Avoiding the ERP feedback effect' leading to price reduction in the referenced country. This is done by maintaining higher local public pricing, competing on market price discounting or even by product withdrawal on the condition that the ERP feedback effect could lead to unaccepted public price reduction in the referenced country and further to a spillover effect in other cross referenced country markets. Agents can re-enter the market if there is no ERP effect or if there is an appropriate change in the pricing regulation.

The mapped agent activity pattern aims to unveil the pharmaceutical firm's ERP related behaviour and their condition/action dependence. The map can also inform the modelling coding process through the links between agent behaviour and the rules and conditions it will be dependent on.

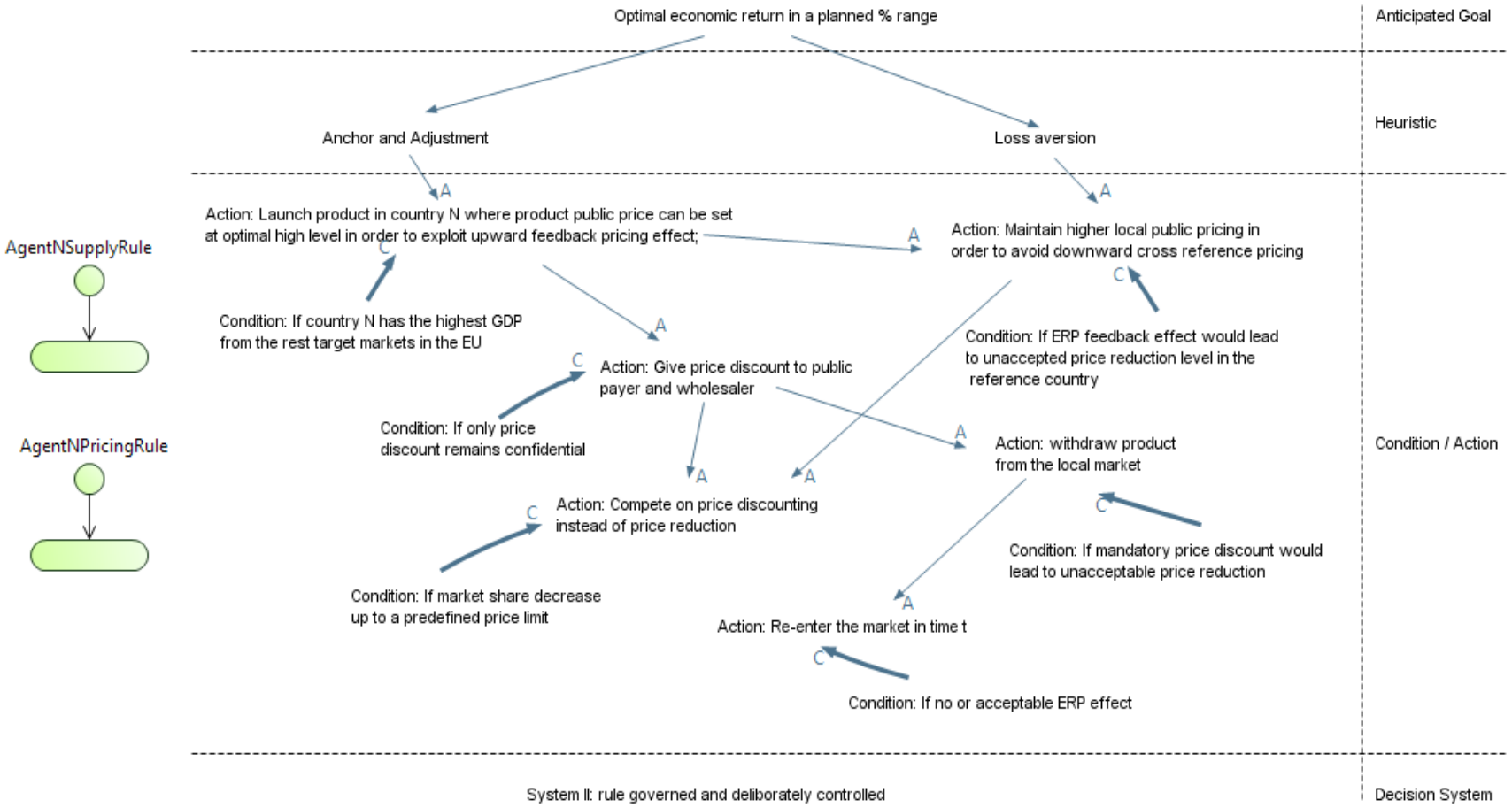


Figure 7.2.9 Agent behaviour map (AbM)

7.3 Integrating Resource/Agent Mapping to create a hybrid RAM

The Resource and Agent Maps were integrated (RAM), with the aim to highlight the main interdependencies among the key market Agents and market Resources in relation to the ERP effect on the pharmaceutical market dynamics. The hybrid RAM analysis presents a rich cognitive model of the pharmaceutical market, driven by a number of important feedback loops and agents forward looking behavioural decision making routines, exhibiting the supply and demand dynamics on a pharmaceutical country market without or with competition (on-patent or off-patent market). Integrating RM and AM supports a comprehensive hybrid exploration of the complex interrelations among market agents and market resources and can be used to become a blueprint for the integration of system dynamic and agent based qualitative and quantitative modelling methodological frameworks, through the identification of the mediation effect of agent decision/action routine on the resource system evolution.

The procedure for designing the maps so far, including enhanced RM, AiM and AbM consisted of the following iterative steps.

Enhanced RM design:

I. Drafting a CoM of main documented statements regarding resources and agents' actions through including coded statements on a white board and drawing connection regarding ERP effects
II. Making a draft of a macro CaM and a micro CaM regarding main resources and links using arrows and signs to denote direction of influence. Drawing stock and flow boxes and arrows over the main resources on the micro CaM and making notes on the map. Making note on main market actors' decisions and linking them to the resources on the map.
III. Making iterative draft versions of enhanced RM in software, transferring main resources and interrelations from the previous drafted CaM into a formal stock and flow diagram including signs for direction of influence.
IV. Elaborating the enhanced RM reflecting on previous maps and notes and on conversations with experts about the RM.

AiM and AbM design:

I. Drafting an initial AiM from reflection on documented statements and previous maps.
II. Reflecting on and drafting decision (condition to action) rules related to each main agent included in the AiM.
III. Drafting an AbM in software and linking with theoretical framework.

RAM design:

I. Drafting an initial resources and agents combined map reflecting on all previous maps and on positions and interrelations of resources and agents within the ERP market system and in respect to the PhD research question.
II. Drafting a RAM in software using graphical notation available in the software tool set
III. Redrafting the RAM after conversations with experts

RM and AM (AiM and AbM) were integrated using the following process:

- Simplify the RM by keeping key resources, inflows, outflows and feedback loops in the modelled system with the influence arrows network realigned;
- Connect the key agents included in the AiM (Agent Interaction Map) to their relevant decision points on the RM by using unidirectional arrows and denoting the decision points by the unified modelling language (UML) sign for a decision branch (a diamond shape);
- Label the arrows connecting the agents with their decision points by the name for their relevant behaviour rule, identified on the AiM (Agent Interaction Map) and explained on the AbM (Agent Behaviour Map);
- Making iterative versions to reflect expert opinion

The combination of the enhanced RM and AbM and AiM to provide an integrated RAM was not straightforward but involved iterative versions guided by the need to keep all important components of all maps but translating them into a unified graphical form. For example, some of the system components appear to have different conceptual and graphical notations in different maps, but in RAM they needed to evolve into a unified conceptual and graphical notation. Another example can relate also to choosing the most relevant graphical symbolization in respect to the novel AbM and AiM and in relation to their transfer onto the enhanced RM in a convenient and clear graphical approach connected to links, labels, symbols etc. components of the graphical apparatus.

The Resource/Agent interaction map's key aim is to elicit the influence of the market agents upon the pharmaceutical system resource configuration through their decision/action routine, and to find where the agent/resource decision intersection points lie. These are denoted on the map by the use of an UML graphical symbol for decision branch for visual comprehension of the key turning points in the resource structure emerging out of agents' activity. The RAM is conceptualized not as a mechanical overlaying of the RM and AM, but as a higher order integrated map which can help further understanding of the endogenous dynamic interdependence among agent decision/action and resource accumulation and depletion, transforming the market system into a system of agent/resource configuration sets. Using the hybrid RAM, turning points of the pharmaceutical market system were found where agents' decision/action rules, which form their behavioural routine, can influence the system behaviour in counterintuitive and nonobvious directions. For example, the drug manufacturer agent decision/action rules related to drug supply, drug pricing and doctor incentivizing could have a turning effect on the ERP purpose to reduce prices by turning the intended vicious feedback loop into a virtuous one through launch sequencing, maintaining higher price, and competing on nonpublic discounting and prescription incentivizing evident in the RAM at Loop R1, Loop R2 and Loop B2.

In the drafting of the RAM, an initial resource agent map was produced attempting to conceptualize a combined ERP market system and interconnections among system components in connection to the PhD research question. Figure 7.3.1.a represents (including Figure 7.3.1.b) that initial draft here, wich main components include the following:

- Agents on the market are price authorities which control national ERP
- Innovative and generic drug manufacturers which make decision to enter or exit chosen local markets and decisions on their local drug´s price influenced through local ERP regulation and through competitive market prices
- Doctors who decide what drug to prescribe, influenced through drug market competition
- Pharmacists who have or do not have decision on drug dispensing
- Patients who decide to follow doctor's prescription influenced through drug price and public funding.

All actors influence the stocks and stock level of the drug supplied on the local market which influence the level of local market competition.

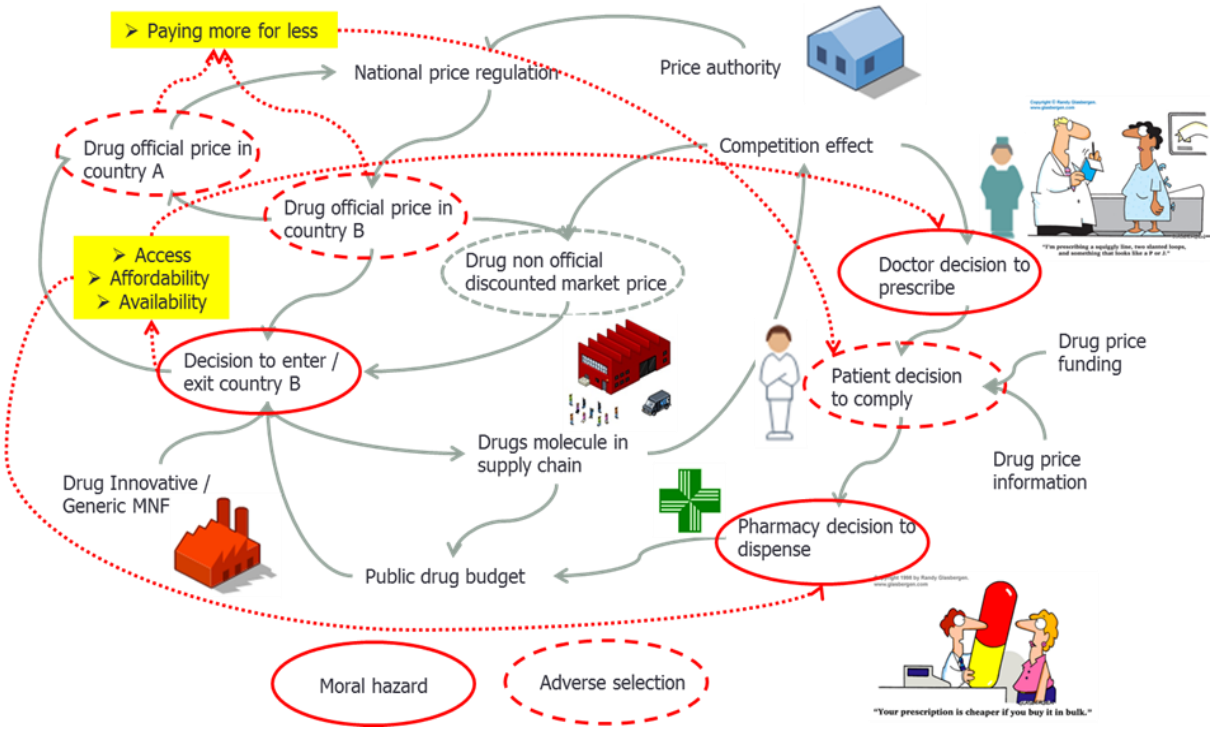


Figure 7.3.1 Initial resource agent conceptualization of a combined ERP market system and interconnections among system components

Figure 7.3.1 represents the initial RAM drafting and reflection on the resource and agents' interrelations in respect to the ERP effect and main criteria for ERP evaluation. That redrafting and notation over the initial draft supported the conceptualization of the positions of and connections among the components of the system, main important decision rules of main agents, main influencing factors and main ERP documented statements from a combined resource agent perspective and from main criteria for ERP evaluation.

Reflecting on all maps before and on the specific hybrid ERP market system, also generated considerations regarding ethical dimensions and regarding affordability vs. availability contradiction like a societal challenge and important public private policy question. Drug companies' decision to supply or withdraw a drug, including overpricing can produce 'moral hazard' and 'adverse selection' phenomena (Arrow 1972, Stiglitz, 2000), all of which are connected to the ERP effects on market resources and agent decisions.

Key considerations elicited by the analysis of the RAM, related to the ERP effect on equitable drug access, availability and affordability on a national and EU wide level, undermining patient medicinal treatment efficiency and health outcome are as follows:

- A medicinal product could have a delayed entry in one EU country compared to another due to an ERP (avoiding circular price referencing, sequential launching and other drug company activities) effect or due to other local pricing regulation, manufacturing capacity or market competition avoidance / rival agreement effect;
- A medicinal product could become temporarily unavailable in one EU country due to a parallel trade effect or due to strategic withdrawal (a market tactic to exit and re-enter with higher price and not to interfere with another country's ERP regulation; or due to competition; or to be redirected to another country market due to a price/volume agreement with the government/payer);
- A product could have a low affordability level (having high reimbursement or high out-of-pocket value) by maintaining higher official and higher actual retail price for longer than it would have been capable of if there were no ERP regulation, in order to generate upward pricing and a circulation effect through a wider ERP application;

The above analysis was supported by the RAM through exploring the possible effect of the agents' condition/action routines on the reinforcing or balancing loops identified in the enhanced RM, having influence on to the key turning points in the RAM. Being able to "see the whole" complexity of the ERP effect through the application of hybrid RAM lead to the advantages pointed out by Ackermann (2012a) such as "(a) ensuring the situation is explored from a range of perspectives, (b) widening the number of alternatives generated and (c) enabling new options to emerge".

Figure 7.3.2 provides a hybrid RAM (Kazakov et al., 2021), exhibiting the map version, achieved after the journal editing procedure and communication with three anonymous journal reviewers.

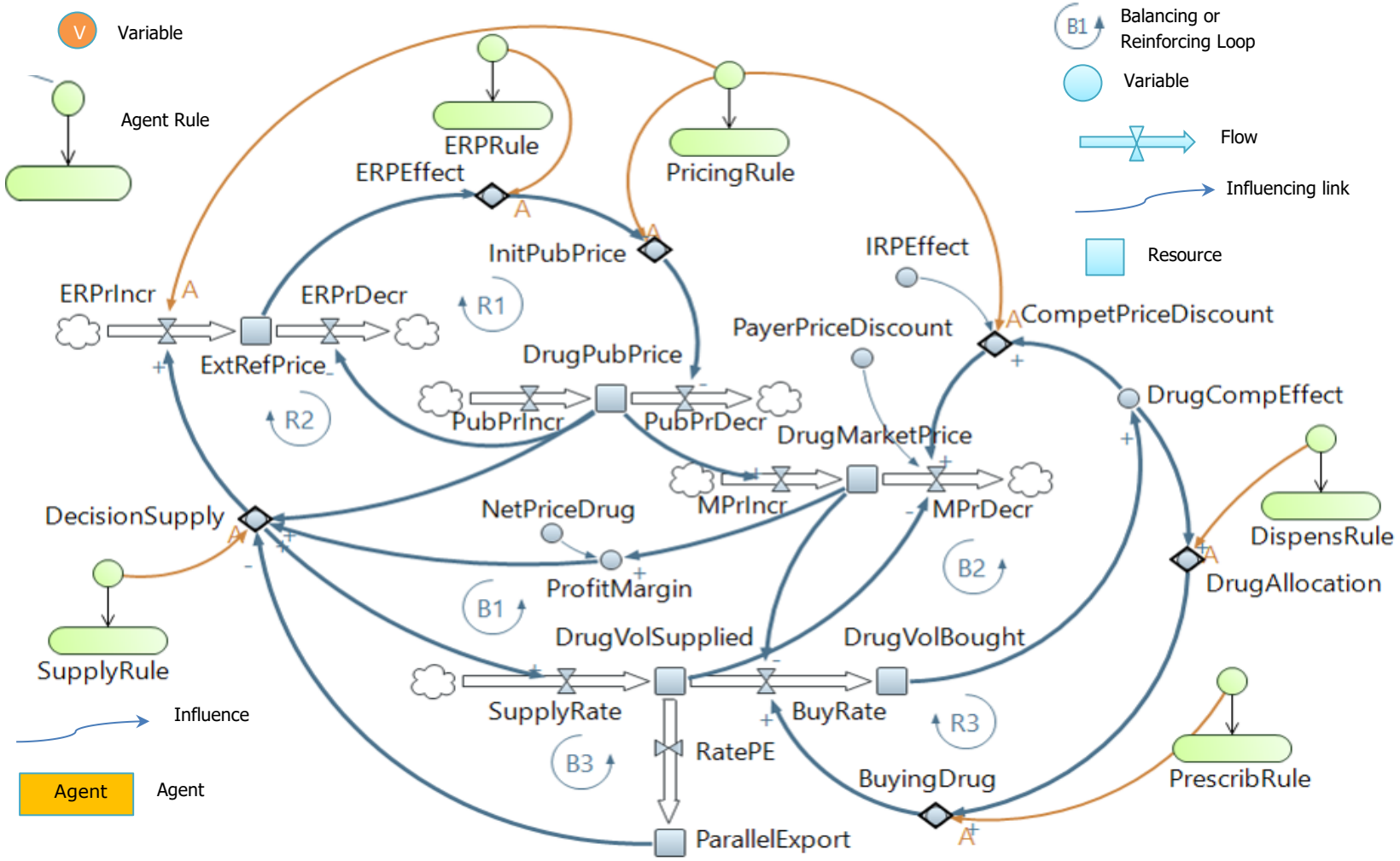


Figure 7.3.2 Hybrid RAM version (EJOR version, Kazakov et al., 2021)

7.4 Scenario identification with RAM

Using the RAM, eight hypothetical scenario cases related to the ERP effect on the pharmaceutical market were identified and are included in Table 7.4.1. It is worth noting that these could also be used for simulation testing as working hypotheses. In general, researchers using a RAM constructed for a specific Resource/Agent system can consider three aspects to generate and explore system scenarios:

- Variation in resource structure of the system (for ERP this was monopolistic or with competition or with or without parallel trade)
- Variation in the researched agent behaviour rules, (for ERP, the rules imposed by the government)
- Contextually related variations (for ERP this includes local differences in prescribing, dispensing and reimbursement regulation), in order to analyze their mediating effect on the agent rule and resource system evolution.

According to the different national market resource structure and government agent regulation rules influencing manufacturing agent condition/action rule and the turning points feedback effect on resource evolution, the authors distinguished different effects on product delay, availability and affordability level. Depending on the type of market system structure, i.e. monopolistic (Loops R1 and R2 on Figure 7.2.11.a and 7.2.11.b) or with competition (Loops B1 and B2), without or with Parallel export/import (Loop B3), the type of External Reference Pricing methodological apparatus (GovernmentAgent ERP Rule), difference in the additional contextual factors linked to market competition such as local pricing regulation, prescribing, dispensing and reimbursement regulation (Loop R3), the effect on market resource and market agent decision/action routine dynamics might differ substantially.

Table 7.4.1 consists of eight scenarios identified following the three steps process described above.

Scenario I explores the ERP regulation effect on a monopolistic drug market, i.e. a drugs market under patent protection. Under such market companies can delay product entry into less attractive countries in terms of local pricing regulation. For example, if there are local mandatory price discounts for reimbursement that could have price decreasing feedback or spill out effect through the ERP mechanism, such countries might experience a delay in product entry and equitable access to drug therapy. The effect of ERP in such market on drug affordability for patients is zero due to the full reimbursement of patented drugs by the healthcare funds.

Table 7.4.1 Scenario insight analysis of the integrated RAM

Scenario	Hypothesis for hybrid simulation analysis
I. ERP in monopolistic market (only patented drugs)	ERP effect on access: delay in product entry; ERP effect on affordability: no effect if reimbursement is full but high effect on the public budget resources; ERP effect on availability: no effect on drug exit;
II. ERP in market with competition (patent and off patent)	ERP effect on access: delay in product entry; ERP effect on affordability: no effect if reimbursement is full; the lower the reimbursement the lower the affordability, i.e. the higher the copayment; ERP effect on availability: effect on drug exit, if price competition is too intensive and ERP cross reference loop could lead to downward price convergence;
III. ERP with Parallel Export	ERP effect with Parallel export : Parallel export does not interfere with ERP regulation;
IV. ERP with variation in pricing methodology (country basket, price calculation by min., average or taking discount into account, reference price revision timing)	A. Including inappropriate countries in one basket for price referencing, could lead to either overpricing or underpricing, B. Price calculation principle based on min. or average without taking into account product volume, including price discount could again misguide price comparison like in A.; C. Regularity and timing of price revision could have effect on price level variation frequency;
V. ERP in INN or branded drug prescription market	ERP country baskets with innovative or generic brand prescription would propagate more inflated prices than country baskets with INN prescription.
VI. ERP in branded market with INN product replacement	ERP comparison among such markets would reach faster price convergence;
VII. ERP in market with variation in reimbursement level	ERP effect on access, availability and affordability is related to price reimbursement level, or copayment level;

VIII. ERP in market with additional pricing regulation (internal reference pricing, price linkage, mandatory discount)	ERP among countries with different local price competitive systems could put an artificial barrier to competitive action by companies in order to prevent spillover effect and thus hinder market competition price reduction effect;

However, the ERP effect on price reduction will be offset by companies' product launch sequencing strategies which can have an upwards effect through the exploitation of the Loop R1 reinforcing cycle in the upward direction. This way, registering at the highest public price in the first country and transferring that price to the rest of the country markets in the launch sequence country basket. In that scenario there will be no effect on product availability due to the lack of price reduction related incentives to leave any local market.

Scenario II explores a market with competition among patented and off patent drugs. The ERP effect on access will be again a delay in product entry due to launch sequencing strategies to exploit the upward reinforcing effect of the ERP regulation. However due to market competition, the effect on access delay should be less than that in Scenario I.

ERP effect on price affordability will be zero if reimbursement is full; the lower the reimbursement the lower the affordability, i.e. the higher the patient copayment. However, depending on the level of competition, the discounted drug market price can increase affordability but will have no connection to the ERP regulation as the public drug price can remain high. The ERP can have effect on drug availability, i.e. effect on drug market exit, if price competition is too intensive and ERP cross reference loop could lead to downward price convergence, if the market price discounts are made public and pricing authorities take them into consideration applying the ERP regulation.

Scenario III explores a market with parallel trade. The ERP effects would stay the same as in Scenario II. However, the parallel drug import/export supports the company's strategy to supply locally higher priced drugs in order not to provide incentive for the parallel traders who profit from local drug price differences. In that way the Parallel Trade appears as an additional factor to the ERP effect, supporting companies launch sequencing strategies and the effect on delaying local drug access.

Scenario IV explores national variations in the ERP application regarding country basket scope, price calculation formula, i.e. by minimum, average and or taking market price discount into account, reference price revision regularity and timing, etc. Including inappropriate countries in one basket for price referencing, could lead to either

overpricing or underpricing effect of ERP, i.e. undermined access and affordability in the former, and access and availability in the latter. If price calculation method is based on minimum or average without taking into account product volume, and or including market price discount could again misguide price comparison and lead to the above mentioned ERP effect. Regularity, i.e. doing more often or less often price revision could have effect on price level variation frequency and accelerate or delay the ERP effects outlined above.

Scenario V explores ERP applied in either INN or branded drug prescription market, would produce an effect similar to monopolistic market structure for the latter leading to cross country propagation of more inflated prices than in a country with INN (MOLECULE NAME) prescription which facilitates retail competition on market prices.

In Scenario VI, related to ERP regulation in a brand prescription market with generic drug replacement/substitution, the ERP effect would facilitate faster downward price convergence among the referenced countries. This is due to the fact that lower priced generic medicines can be substituted for higher priced originator branded medicines.

In Scenario VII, which explores a market with variation in reimbursement level, the ERP effect on access, availability and affordability would be related to price reimbursement level, or patient copayment level. The higher the level of reimbursement the lower would be the ERP effect on access, patient level affordability and availability and vice versa.

Scenario VIII is regarding ERP regulation in a market with additional local pricing regulation, i.e. internal reference pricing (IRP) for drugs with the same molecule, price linkage percentage between the original and the generic drug, mandatory price discounting for reimbursement. IRP can be applied by drug molecule, i.e., only reimbursing the lowest priced molecule, whether an originator or a generic. This is the situation in e.g., Sweden with compulsory generic substitution of the lowest priced molecule, with the patient having to cover the costs for the more expensive medicine (e.g., an originator) if they wished a more expensive molecule. This had an impact on appreciably reducing the price of a number of generics (Godman et al 2009). IRP can be applied also on the level of therapeutic class or on the level of the disease area.

ERP application among reference countries with different local price competitive systems could put an artificial barrier to competitive action by companies in order to prevent external reference price spillover effect and thus hinder market competition and drug price reduction effect.

The above demonstrates that a full evaluation of the ERP effect should take account of local market structure and drug regulatory specifics, and that a hybrid SD/AB simulation

interactive learning environment could further enhance researchers and policy makers capacity for the analysis and evaluation of the ERP regulation effect on drug equitable access, affordability and availability. The use of such a hybrid simulation modelling technique would provide means for rich scenario testing with the capacity to inform further a more efficient and sustainable drug pricing regulatory environment.

7.5 Discussion and future potential for RAM applications

Combinations of agent based and resource-feedback approaches have traditionally been carried out from the individual perspectives of resource structure or agent behaviour, or opposing macro to micro, quantity of stock levels to quality of agent behaviour patterns, and resources to agents, and without the application of a joint conceptual/qualitative hybrid model building procedure, leaving calls for hybridization of both SD and AB unattended from conceptual and theoretical perspectives (Guerrero et al. 2016b; Hans Jochen Scholl 2001; Schieritz 2002).

In addition to the application of the RAM as a novel problem structuring tool, the enhanced RM and the novel AM techniques can be applied either individually or in an integrated RAM tool as a hybrid qualitative conceptual modelling procedure. Conceptual modelling is acknowledged to be a key tool for model validation and confidence building in health care and aims to help the structural modelling and validation (Roberts et al. 2012) procedure. Validation and confidence building focuses on the correspondence between the real world phenomenon under examination and the simulation model (Marshall, Burgos-liz, et al. 2015) in an iterative transparent and visualized processual way (Law, 2009) with the aim of ensuring there are no qualitative and quantitative (Eddy et al. 2012) difference. A hybrid RAM can have the capability to strengthen the integration process between the two modelling approaches and the confidence building among modellers and users (Howick et al. 2008; Borschev 2008; Macal 2010)

The above demonstrates that a full evaluation of the ERP effect should take account of local market structure and drug regulatory specifics, and provide opportunities for designing a hybrid SD/AB simulation interactive learning environment. This could enhance further the researchers and policy makers capabilities for the analysis and evaluation of the ERP regulation effect on drug equitable access, affordability and availability. The use of such a hybrid simulation modelling technique would provide means for rich scenario testing with the capacity to inform further a more efficient and sustainable drug pricing regulatory environment.

In addition, the AM could be applied to enhance the agent based conceptual model building and validation process, in relation to more accurately collecting and interpreting data and analysing agent behavioural and decision making pattern. This process is enhanced through taking into account the behavioural decision and anticipatory systems theoretical perspective proposed here. Applying RAM as a novel hybrid tool for conceptual qualitative modelling and as a blue print for quantitative hybridization of SD/AB modelling approaches, can further reveal new theoretical, methodological and practical avenues for research. This can allow for a focus on more comprehensive integration of the two methods, and on the behavioural exploration of complex adaptive systems.

The development of the novel AM technique and its mixing with extended RM in a hybrid RAM is limited to their application in the pharmaceutical market field and would benefit in the future from other attempts to expand its application to other complex market systems in health care and different socioeconomic domains rich in resource and agent complex interactions. Also, they could be employed to treat issues related not only to market regulation but also to market competition in relation to operational and strategic management of resources, behavioural stakeholder/agent management etc.

Integrating SD with AB modelling and simulation will provide extended benefit to understanding complex systemic behaviour of the pharmaceutical market due to the combination of two modelling approaches which address both dynamics on a whole system-macro and individual micro agent-behaviour perspective. Testing what if policy changes in a constraint healthcare environment can reveal hidden gaps, information asymmetries and key leverage points for optimal policy decision making /limitations in budget, reimbursement pricing along the supply chain, limitations in information, access to treatment and co-payment, level of therapy compliance, supply chain imperfections, etc./. The outcome of the RAM exercise produced a rich cognitive picture of the agent/resource pharmaceutical market dynamics. ERP regulatory regime clearly could be viewed to be a device for "unveiling the curtain" in front of the product market prices in EU with the goal to facilitate global price downward convergence and price affordability. However, attempting to lower information imperfection by maintaining a common price data tool for international referencing, could produce opportunity for a pharmaceutical company to exploit the regime by double pricing, i.e., one higher price for the public record with optimal premium to "feed" the ERP procedure throughout the EU, and one for the real market to maintain optimal competitive advantage; a practice ultimately leading to upward price convergence. The above can lead to even greater difference between social returns and private returns.

The key battle between economic agents, following Stiglitz (Stiglitz 2002), is over controlling access to rents and over restructuring of markets and rules, which limit the

public economic return on healthcare expenditure. Attempting to eliminate information imperfections in relation to product pricing transparency across EU member countries by the application of ERP can lead to further price information internalization and exploitation of the regulatory system by the pharmaceutical companies (Stiglitz & Jayadev 2010), further information imperfections, hindered price competition and higher global market complexity and local market fragmentation. Explanations of the real economic environment complexity due to mutually inductive interactions and information feedbacks between pharmaceutical market agents' behaviour and limited market resources could benefit from qualitative modelling analysis techniques like extended resource mapping (RM) and agent mapping (AM) alone and in combination through a hybrid resource/agent mapping (RAM) approach as the authors have demonstrated.

Inefficient drug price controls, which are limiting market competition and the effect of competitive pricing regulation, have the effect of providing means for maintaining or even increasing the price of pharmaceuticals, without leading to an equal public economic return. The structure of the pharmaceutical product market system is based on information imperfections related to patent protected drug data and to differential drug prices across different country markets (Stiglitz & Jayadev 2010). Private returns and product demand are fostered by the exploitation of the above market imperfections and a growing need is acknowledged for a proper evaluation of pharmaceutical regulation in relation to key healthcare goals of timely access, affordability and availability of medicinal products (Council of the European Union 2016) EC report on pharmaceutical market efficiency. The integrated RM and AM analysis of the ERP regulation clearly demonstrated that aiming to enhance price transparency and reduce drug prices could, contrary to public policy intention, lead to further level of information imperfection due to differential pricing information internalization and price launch tactic by the pharmaceutical companies in order to exploit the ERP reinforcing loop cycle for global price inflation effect, in attempt to maintain optimal margin and higher economic return for longer period of time.

Chapter 8 Hybrid SD & AB quantitative simulation model building

8.1 Purpose of the hybrid SD & AB simulation modelling

The purpose of the hybrid SD&AB quantitative simulation modelling is to transform the qualitative RAM into a numerically and operationally sound representation of the research question on the evaluation of the ERP effect on drug access, availability and affordability in EU. In this respect, the hybrid simulation must be built with the capability for scenario experimentation for simulation testing of the qualitative scenarios generated by the RAM, analysis of the simulation results and for developing policy recommendations.

The novel RAM developed in previous chapters is applied as a conceptual procedure for hybrid quantitative model building and as a functional specification for the coding of the simulation model resource structure and agents' behavioural routine.

It should be noted that so far, no ERP simulation has taken into account behavior of main market agents and their interrelations with market resources, and interfering effect of contextual regulation. The only simulation on ERP published is very limited due to its isolated focus on ERP mechanism (Toumi et al., 2014) without taking into account the above-mentioned gap.

8.2 Software used for hybrid simulation building

Anylogic (XJ Technologies) software has been chosen for quantitative hybrid simulation due to its capability to handle multimethod modelling and simulation, namely combination of a SD macro with an AB micro perspective.

In the above respect, Anylogic software is capable to support mathematical (continuous) with java programming (discrete) simulation integration, providing flexibility in respect to any type of SD & AB combinations (Borshchev and Filippov, 2004).

Anylogic technical functionality allows application of agent classes, and multiple types of agents and structures. Agent behavior modelling is supported by visual tools like state charts and action charts. The software also has full features for SD stock and flow diagrams, and supports SD simulation. It allows control over continuous and/or discrete time, continuous and/or discrete space, agents' mobility, and communication between agents (e.g. message passing). Another important feature is its relatively small memory

requirements and capability to export simulation models online or as standalone applications (AnyLogic Professional). It is provided as a free version for personal learning (AnyLogic PLE), which of course has restrictions on functionality and scope, as a paid version for academics and as a fully functional paid version for professional purpose.

8.3 Hybrid SD and AB simulation modelling procedure

Figure 8.3.1 represents simulation design procedure main stages. These are I. Conceptual specification, then II. Functional specification, then III. Technical specification. These stages are elaborated throughout the whole PhD document and provide a fuller documentation on the simulation design from its initial conceptualization phase, to description of the simulation functions phase, to the implementation in technical software code phase (Sargent, 1998; Djanatliev et al., 2012; Kolominski – Rabas et al., 2015). In comparison to the 'overview, conceptual design and details' (ODD) procedure applied for ABM simulation design (Macal and North, 2010; Grimm et al., 2010), the 'conceptual, functional and technical' specification procedure provides full documentation capturing all the components of the hybrid system dynamics and agent-based simulation designs and can support simulation confidence building (verification and validation), including reproducibility requirements better than the ODD practice, which ensures mainly requirements for the simulation technical verification without maintaining the requirement for explaining the connection with the simulation conceptualization phase (which is essential for confidence building and validation purposes).

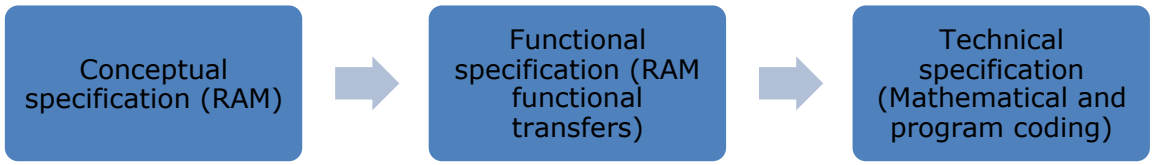
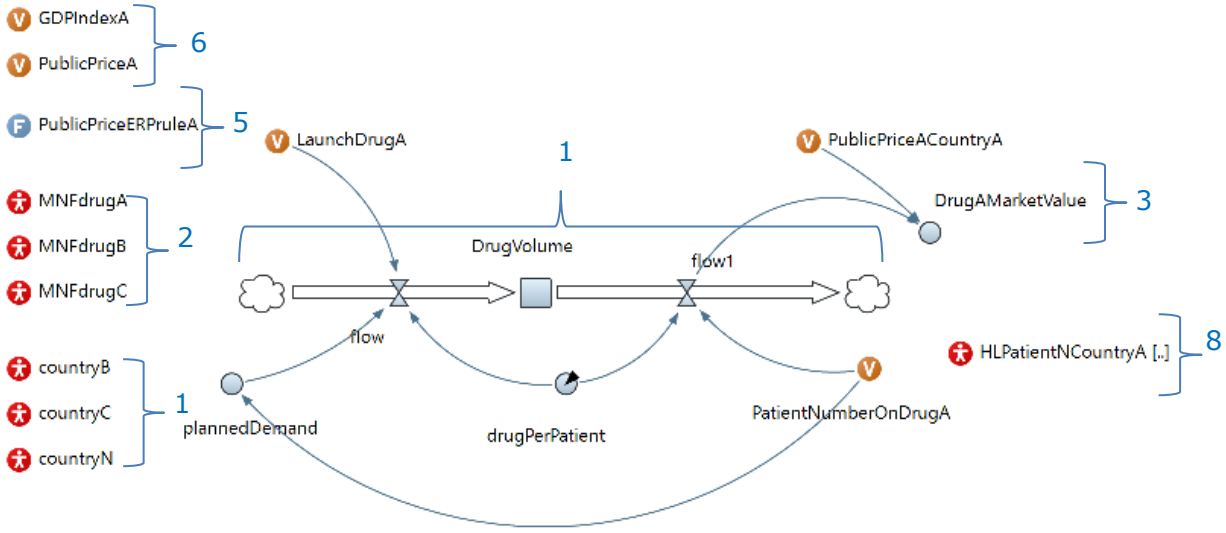
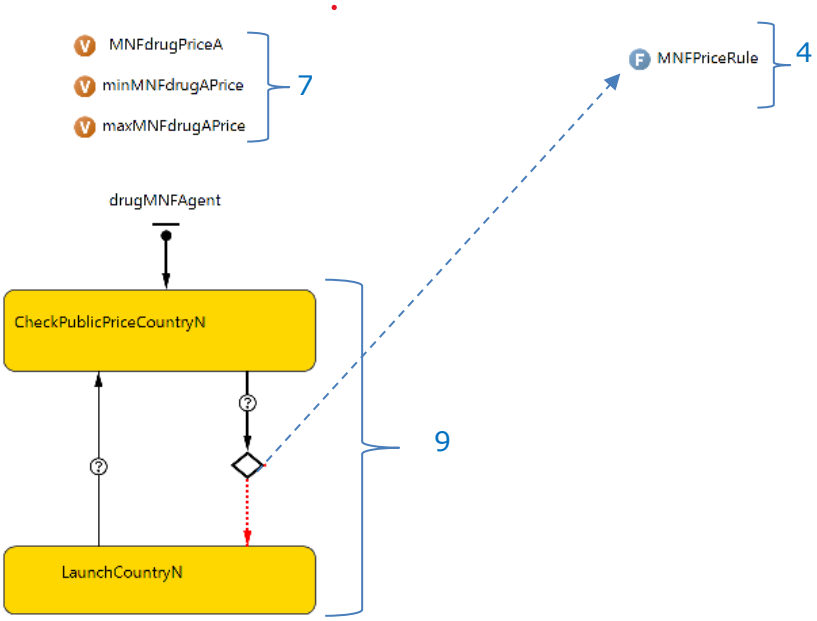


Figure 8.3.1 Simulation design procedure

The functional specification of the ERP hybrid simulation is tightly linked to the hybrid RAM. The RAM now is used as a hybrid quantitative simulation building procedure (Ackermann et al., 2014), apart from its qualitative analytical merit, bringing a comprehensive perspective to the management of CAS.

The procedure of building a hybrid SD and AB simulation model followed a number of steps aiming at translating the RAM into a formal functional and technical specification of the quantitative model. The functional specification included the transfer of the qualitative RAM to a description of the main SD and ABM components' functions, i.e. stocks and flows of resources for the first and agents, their attributes and their behaviour for the second, including main connected parameters and behavioural assumptions characterized in tables. It is explained in section 8.4.





Legend:

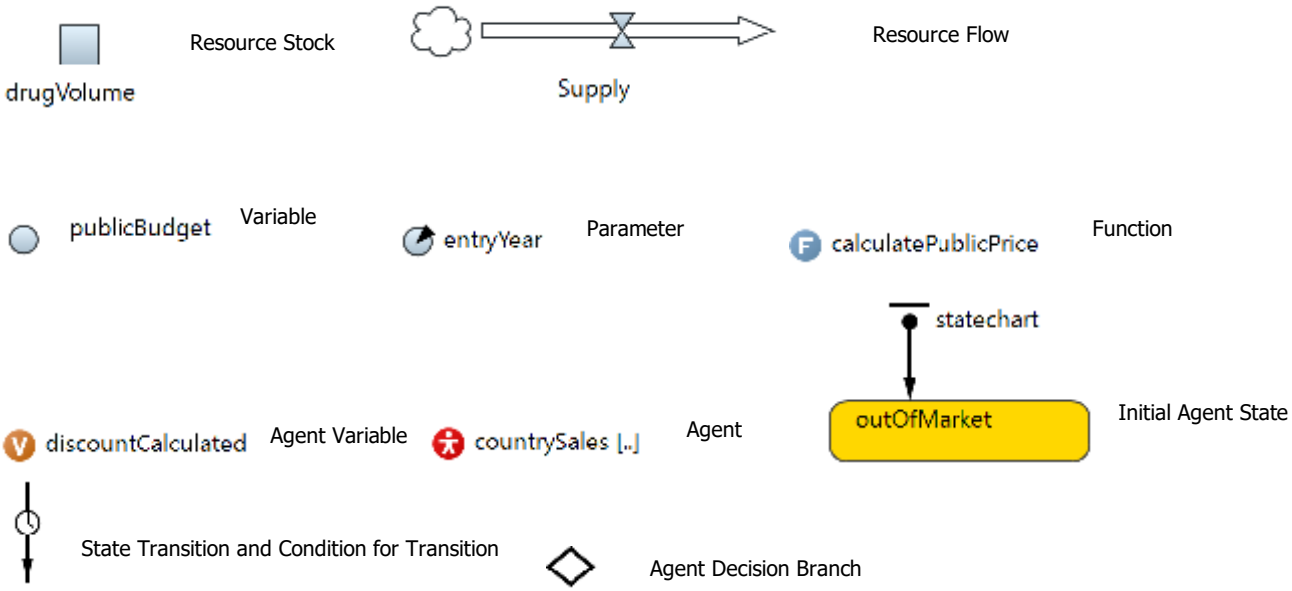


Figure 8.3.2 Reflecting on the procedure of transferring the RAM conceptualization of the ERP market system into a technical software specification for the hybrid SD and AB design

Figure 8.3.2 presents a reflection on the procedure of transferring the RAM (Figure 7.3.2) into a software technical specification. Initially, main resources and resource flows were taken from the RAM and, together with main agents and related parameters (and attributes), have been initialized in graphical, mathematical and program code (Figure 8.3.2), following the principle 'from simple to complex' components and interconnections (Ghaffardezegan et al., 2011, Gilbert et al., 2018). Then, the next step included testing, reflection and editing resource and agent simulation model structure, allowing for conceptual and technical corrections, in order to reach to a maximally close technical representation of the RAM.

Figure 8.3.2 reveals the initial reflection over the RAM technical structure transfer into software:

- the drug supply chain (SD component) was technically reconceptualized to provide separate (individual pharmaceutical firm agent) supply chain for each drug (drugA, drugB, drugC, etc.), similar to the SD notion for using 'subscripts' (component 1 on the Figure 8.3.2)
- this followed to further accounting for market price competition, produced between all drugs (component 2)

- further, this led to variables addition for 'drug market value' (linked to specific pharmaceutical firms pricing strategies, connected to changes in their market share, component 3)
- MNF drug price and entry strategy was conceptualized as an agent decision function (component 4)
- Another reflection was made, related to 'PublicPriceERPRuleA' rule of the pricing authorities (government), which need to check drug public prices in other countries depending on their ERP price baskets (component 5). This ERP rule was conceptualized as an agent decision function.

Other considerations included agents' behaviors:

- drug manufacturers agents ('drugMNF') were initially conceptualized to have one innovative and two generic drug suppliers and to variate in number (component 2)
- 'government' agents were conceptualized to have main attributes of GDP and ERP baskets (component 6)
- Also, MNF drug agents were conceptualized to have drug price associated variables of min and max thresholds (component 7)
- 'patients' are conceptualized as agents which buy medicines following specific rules (component 8)
- Drug MNF agents were initially conceptualized to have two states (component 9): out of the market (checking drug public price in the ERP countries) and being on the market (launching their drug on a local market)

Next, the technical specification included the building of stock and flows diagrams and coding of mathematical equations, representing the relations between the SD elements (resource levels and resource flows, parameters, variables and feedbacks); and the coding of agents' state charts and or actions' charts related to their ´IF THEN´ behavioural algorithm and their attributes (state variables) in the programming language of the software used (here it is java which is the programming environment of Anylogic PLE). The technical specification is explained in section 8.5.

8.3.1 Data sources

The functional and technical specification have been done using the qualitative data collected and applied for the RAM design, including scenarios and insights generated by the use of the RAM. The approach is briefly restated here:

Information regarding the ERP context was collected through written documentation output such as the EURIPID report (Schneider 2017), pharmaceutical industry position letters, author observation and participation in drug industry working group meetings and meetings with health care regulatory authorities. The goal was to use the data collected from document analysis (Barr et al. 1992), minutes of meetings and industry position papers (Huff & Schwenk 1990; Barr et al., 1992), conversations, researcher notes and reflection (Ackermann 2012; Ackermann & Eden 2011; Eden & Ackermann 2004), for the mapping of the mental models (Doyle & Ford 1998; Carley 1997; Jones et al. 2011) of key stakeholders in the pharmaceutical market, i.e. the pharmaceutical industry and drug pricing regulators.

To extract relevant information, I have used a theory led thematic analysis (Hayes 1997) protocol, consisting of looking for and elucidating meaning connected to the following themes:

- Key resources and key agents in the pharmaceutical market system;
- External reference pricing (ERP) regulation effect on the pharmaceutical market system, in relation to drug access, affordability and availability;
- Key agent/resources and agent/agents interrelations, including the main influencing factors affecting resource levels and flow rates and agent behavioural routines;
- Key agents and resources behaviour in relation to ERP regulation and other contextual pricing and market regulation;
- Agents' behavioural routines (agents' "if/then" condition action rules), in relation to the effect of ERP on their pricing strategies

8.4 Functional specification of the hybrid simulation modelling

Following the key resources and agents' interrelations presented and analyzed in the RAM, the following agents, resources, related parameters, state variables (attributes) and assumptions have been further specified in tables (Table 8.4.1, Table 8.4.2, Table 8.4.3, Table 8.4.4).

Table 8.4.1 of main agents, agents' parameters, state variables (attributes) and agents' behavior (functions) in the hybrid simulation:

Agents	Agents' main parameters and state variables (attributes)	Agents' main functions (behavioural routine)
Pharmaceutical firmss, manufacturing innovative and generic medicines	Name; Number; Maximum (desired) price; Minimum (threshold) price; Entry year; Market share; Marketing allocation; Condition for price decrease depending on market share;	Supplying (launching) in EU countries, starting from most attractive one (with highest GDP); Calculating market share; Marketing budget allocation; Changing product price due to competition;
Parallel traders	Name and number; Country where they buy drugs from; Entry year; Time to investigate drug market prices; Market share;	Investigating drug markets and prices differences; Buying from country they are located in; and selling to country with highest price difference;
Countries	Name and id number; GDP index; Public price policy (min. or average calculation); Time period to review and change Public price;	Calculating Public price, according to price formula, time period and country basket selection;

	Countries used in the reference price basket; Regulation for prescribing (by innovative or generic branded drug or by molecule);	
Doctors	Doctor population (number); Allocation of hyperlipidemia drugs by innovative or generic brand or by molecule;	Prescribing (allocating) drugs to hyperlipidemia (hl) patients, according to type of prescribing regulation (by innovative or generic brand or by molecule) and to marketing budget influence of pharmaceutical firmss;
Patients	Hyperlipidemia (hl)patients population; Consumption of drugs per month;	Buying drugs allocated by doctors (if prescribed by innovative or generic brand) or buying available drugs according to price (if prescribed by molecule);

Table 8.4.2 of main resources (stocks) and resource flows in the hybrid simulation

Main Resources (Stocks)	Inflows and Outflows	Variables influencing resource level
Drugs supplied to country market	Rate of supply and rate of demand	Planned demand per year; Decision to supply (launch); Public price
Drugs bought by patients	Rate of demand (consumption)	Competition (number of drug suppliers);

		Consumption per year; Number of patients; Demand for relevant drug; Marketing budget; Market share; Prescribing regulation (by innovative or generic brand or by molecule);
Drugs bought by parallel traders	Rate of PT buying	Public price difference among ERP countries;
Drugs sold by parallel traders	Rate of PT selling	Demand for relevant drug; Prescribing regulation; Public price;
Drug's Public price		ERP country basket (number and combination of selected countries); Public price calculation formula (average or min); Time period of Public price recalculation; Prescribing regulation (by innovative or generic brand or by molecule); Drug price competition (number of drug suppliers and pricing strategies);

Table 8.4.3 of main parameters in the hybrid simulation related to scenarios setting and experimentation (parameters variation)

Parameters	Scenarios
Number of drug manufacturing agents' (innovative or generic)	Variation of the level of competition: from one drug (on patent, monopolistic market) to two, three or more rival drugs (off patent market)

Minimum and maximum drug price	Variation of the level of target profit margin, for example, maximum price = 10 monetary units; min. price = 5 monetary units
Time of entry of innovative or generic drugs	Variation of period of patent protection, for example 15, 10, 5 years
Marketing strategy (marketing allocation condition)	Variation of % allocation from sales for marketing budget, for example, 15%, 10% or 5% or other
Pricing strategy (price decrease condition)	Variation of % of price decrease related to variation in product market share, for example, decrease price with 15%, 10% or 5% or other, if market share is less with 10% or other
ERP country basket	Variation in number and combination of price reference countries in the ERP basket, for example, 15, 10 or 5 countries basket, containing different ERP Countries for each experiment
Public price formula	Variation in Public price calculation: referring per min. or per average price of the same drugs among a reference countries basket
Time period for Public price revision and recalculation	Variation in time period (for example in 1 or 2 or 3 years)
Prescribing regulation	Variation in prescribing regulation: by innovative or generic brand or by molecule
Number of parallel traders	Variation in intensity level of parallel trade (number of parallel traders among ERP countries: 5, 10, 15 or other)

Table 8.4.4 of main assumptions

Main Assumptions related to resource agent interrelations	Notes and justification

It is a pharmaceutical external reference pricing model with a simple supply chain in all EU (EEA) countries applying the ERP or included in the ERP mechanism. o Three drug MNF agents decide in which country to launch their drug, depending on each country GDP index. They launch first in country with highest GDP index, which is the most attractive country market, setting price to their max desired price if they are first supplier. Public price regulation (which compares the drug price with an ERP basket of countries' prices for the same drug and calculates the average or minimum value for that price) is set to reflect the actual situation in Europe. o The three drug MNF compete on drug market value (market share) and if it decreases by 10% for an MNF agent, then that MNF would decrease their drug's price by 10%. o Patients buy the cheapest drug available in a country, or they can buy a certain drug brand (if prescribing regulation is by molecule or by innovative or generic brand). o If the MNF drug Public price becomes equal or below a predefined MNF min drug price (threshold), then the MNF agent would stop supplying the drug. o If a country price is equal or below the predefined min MNF drug price, then the MNF agent will not start supplying the drug.	All ERP related parameters per country are set to reflect the actual situation (reference country baskets, price calculation formula, time period for price review) and are referenced to ERP surveys (Vogler, S. et al., 2015; Toumi, et al., 2014). Pharmaceutical firms supplying, pricing and marketing strategies (market behaviour) reflect published research (Schneider, 2017; Vogler, S. & Paterson, K.R., 2017 , and RAM analysis and theoretical framework. Pharmaceutical firms have a predefined (anticipated) goal profit margin, according to which they set their max. desired drug price. First pharmaceutical firm registers their max (desired) price in the most attractive country market. Then they adjust their price in other countries according to the local public price and competition, reflecting BDT heuristics principle of price "anchoring and adjustment". A pharmaceutical firm exits a country market if the local Public price decrease to their min. price threshold, reflecting BDT heuristic principle of profit margin "risk aversion".

> Doctors allocate (prescribe) a branded drug of a certain company; for example, drugA of drugfirmA or drugB of drugfirmB etc. either randomly or influenced by each pharmaceutical firm marketing budget in such a way that a doctor would allocate with high % probability the drug of the pharmaceutical firm with highest marketing budget. > Or a doctor agent can allocate (prescribe) a nonbranded drug (drug molecule), which means that the patient can choose which drug to buy on the market: drugA, drugB, drugC etc. (randomly or the cheapest, for example); > If a pharmaceutical firm marketing budget is higher than the other pharmaceutical companies marketing budgets, then doctor agents will prescribe that drug with a higher probability (for example 80%); > Pharmaceutical firms can have two general market strategies (if they are losing market share): they can try to win doctor agents by increasing their marketing budget with random (min, max) percentage of product sales (when in the country there is a Prescribing Regulation by brand), or they can try to win patient agents by decreasing drug price with a chosen percentage (if the Prescribing Regulation is by molecule); or they can combine both of the above; > Patient agents buy the drug (drugA, drugB or drugC) which the doctor agent allocated (if by brand);	Doctors and patients behavior reflect two main general situations related to the state of prescribing regulation (by brand or by molecule). Pharmaceutical firms compete either through marketing budgets targeting doctors and or patients (if prescribing by brand), or through price decrease (if prescribing by molecule);

> Or they can choose to buy a cheaper drug with a predefined probability (if prescribing by a drug molecule);	
Parallel traders buy cheaper drugs from one local market and export them to the local market with highest difference in drug price. They have their own "parallel" supply chain which affects the relevant drug volume supplied by drug manufacturers and drug volume bought by patients. This in turn affects pharmaceutical firms pricing, marketing and supplying strategies related to each local market.	Parallel traders' behavior reflects published research (Vogler et. al, 2015, Bart, 2008, Kyle, 2009, Affordable Medicines Europe, https://affordablemedicines.eu/mission-and-vision/

8.5 Hybrid model conceptual validation

Conceptual validation of the hybrid simulation modelling (if I am building the right simulation model) is achieved through the continuous process of building, first a qualitative hybrid RAM, which in the next second stage, is transferred into a fully functional hybrid simulation modelling specification. Resources and agents' interactions, including influencing factors (variables and parameters) have been functionally specified (defined) in the above tables, following their graphical description and analysis on RAM, including key "decision points", agent interactions and behavioral rules, and resource agent feedback loops.

Also, the functional specification is not only a conceptual twin of the validated RAM through documentation and expert views analysis (Heath et al. 2009), but is consistent with its theoretical framework and with actual documented observation, related to agents' and resource interactive behavior (Randers, 1980; Ormerod and Roswell, 2009; Bonabeau, 2002)

Using the qualitative RAM as a tight procedure for the specification and building of a hybrid simulation model ensures that the right model is being built and a conceptual validation is achieved (transferred from qualitative to quantitative model). This can be

proved by comparing the RAM with the hybrid simulation model representation in software, showing a sufficient structural and logical similarity between both. The procedure of RAM transfer into a quantitative simulation structure is explained in section 8.3 and continues throughout this chapter 8.

8.6 Hybrid SD & AB simulation (technical specification) coding

8.6.1 Medicinal products supply chain (SD)

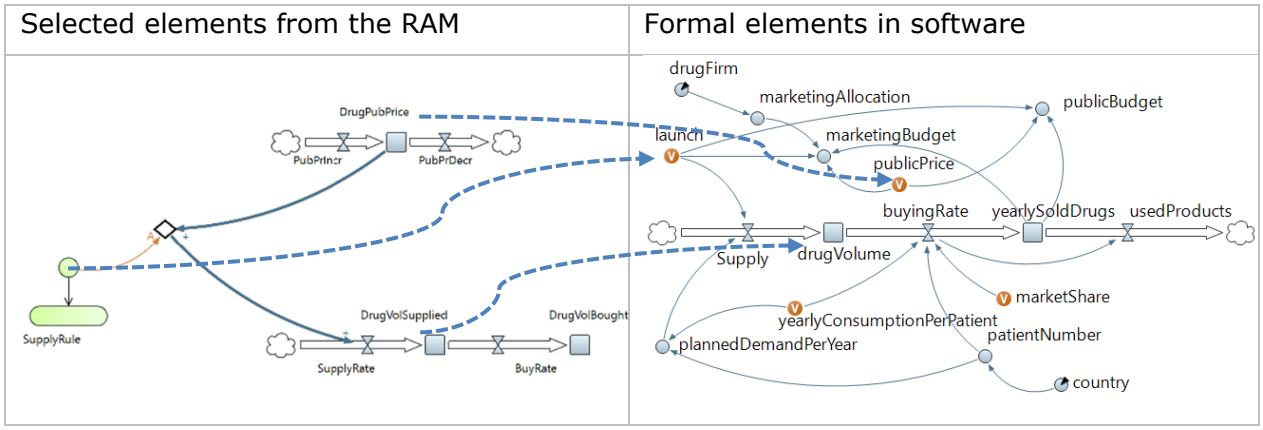
Initially a simple medicinal product supply chain is built, using the SD functional panel of Anylogic software. This supply chain is informed by the RAM developed in the qualitative modelling stage of the ERP evaluation project, which followed a reflection procedure of technical transfer initialization, correction and adjustment, presented on Figure 8.3.2. It is placed inside an agent type named "Country sales", which would correspond to each pharmaceutical firm stocks flows of medicines supply and medicines sales in each country, where the product would be launched (Figure 8.6.1.1).

Figure 8.6.1.1 exhibit, as an example of the technical transfer procedure, selected elements from the RAM on the left side, and elements of the technical software design on the right side. The blue arrows have the purpose to visualize what elements from the functional specification (represented by the RAM) have been transferred to what elements from the technical specification.

For example, the drug supply chain from the RAM has been transferred almost within the same simple drug supply chain in the software, with related variables associated with the flows of the drugs on the market. Pharmaceutical firm agents' supply rule has been translated to code which affects the decision to launch a new drug in a selected ERP market. Drug public price has been transferred from a stock and flow representation to a dynamic variable, which depends on agents' pricing rules.

The transfer of the RAM into a functional software application followed a number of steps and iterations including software drafting design procedure and numerical verification tests. Later a number of versions were produced, followuing changes and clarifications in conceptual requirements connected to the evaluation of the ERP effects, generated qualitative scenarios and main criteria for evaluation.

Figure 8.6.1.1 Drug supply chain transfer links between the RAM and the software technical specification (for one country market and one drug manufacturer), valid for each local country market and each drug supplying manufacturer



(8) The supply chain consists of a "drugVolume" stock of supplied medicines and a "yearly Sold Drugs" stock of sold medicines in each country market. The level of the first is a function of the supply rate inflow ("Supply") and the buying rate outflow ("buyingRate"), represented in equation 1:) "drugVolume" = Integral ("Supply" – "buyingRate", 0)

The level of the second stock is a function of the buying rate ("buyingRate") and the rate of drug usage per year ("usedProducts"), represented in equation 2:

(2) yearly Sold Drugs = Integral (buyingRate – usedProducts, 0)

The supply rate ("Supply") is a function of the Boolean variable "launch" which corresponds to the key decision point in the RAM, relating to each drug manufacturer's decision to enter or not to enter a country market, and the variable "plannedDemandPerYear" (equation 3):

(3) Supply = launch*plannedDemandPerYear

The "launch" variable can take a value of either "0" or "1" (equation 4), and is dependent on a programmable function (agent's rule) of the pharmaceutical firm agent behaviour, while plannedDemandPerYear depends on the number of patients taking their drugs and yearly consumption per patient (equation 5):

(4) launch = 0 (initial value)

(5) plannedDemandPerYear = patientNumber*yearly Consumption PerPatient

The buying rate ("buyingRate") is a function of the number of patients, the number of packs they need per month (year) and on each pharmaceutical firm's market share per country market (equation 6):

(6) buyingRate = patientNumber*yearly Consumption PerPatient*market Share

The market share of each pharmaceutical firm agent is calculated by an equation put in programmable code, counting total number of patients and number of patients buying a certain drug per country, and then relating the latter to the first (equation 7), providing total number of patients is not 0:

(7) market Share = count(country.hl Patients, p -> p.drug !=null) == 0 ? 0 : (double) count(country.hl Patients, hl -> hl.drug. equals (drugFirm))/count(country.hl Patients, p -> p.drug!=null)

The variable "patientNumber" gets its value by the following equation in code (equation 8), related to counting patients' size per each country:

(8) patientNumber = country.hl Patients .size()

The yearly consumption per patient is defined by the time period between drug packs bought by each patient (equation 9);

(9) yearly Consumption PerPatient = 365/main.time Between Drugs(DAY)

An important variable, related to drug manufacturers competition strategy and having a feedback effect on pharmaceutical firms market share, is the marketing budget ("marketingBudget"), presented in equation 10:

(10) marketingBudget = launch*yearly Sold Drugs*(publicPrice==infinity ? 0 : publicPrice)*marketingAllocation

The initial value of publicPrice is set to "infinity", which means an initial undefined value due to technical requirements of the software, in order to eliminate 'null' exception error if initial drug price equals '0' value rather than 'infinity' value (technical requirement of java programming language). Marketing allocation is a parameter, relating to each pharmaceutical firm marketing strategy, defined in the variables and parameters table for the pharmaceutical firm agents.

8.6.2 Pharmaceutical firm agents' behaviour (AB)

The behavior of pharmaceutical firm agents is configured by using state charts and agent parameters and state variables, with the purpose of defining their activity states and

their specific attributes. It is informed by the AiM and AbM, which are part of the RAM and consists of a more detailed functional depiction of agents' behavioural rules and their interrelations.

State charts in AnyLogic are used to support defining main agents transition from one state to another. Regarding pharmaceutical firm agents, state charts are used to transfer and define their 'supply rule' while functions are used for the specification of their 'pricing rule', 'marketing budget allocation rule' and 'drug withdrawal rule', presented in Figure 8.6.2.1, Figure 8.6.2.2, and Table 8.6.2.1 and 8.6.2.2, including pharmaceutical firm initial variables in Table 8.6.2.3.

Pharmaceutical firm agents have a name, minimum and maximum defined drug price boundaries (setting their min. price threshold and maximum desired price), year of market entry (launch), conditional value for price decrease depending on a predefined percentage value of market share decrease, and a percentage predefined value for marketing allocation. These parameters are defined in a table in excel sheet and imported in the simulation model database (Figure 8.6.2.1 and Table 8.6.2.1). This parameters table allows for their variation and for setting scenario experiments, including adding more or less pharmaceutical firm agents (increasing or decreasing the level of market competition).

Figure 8.6.2.1

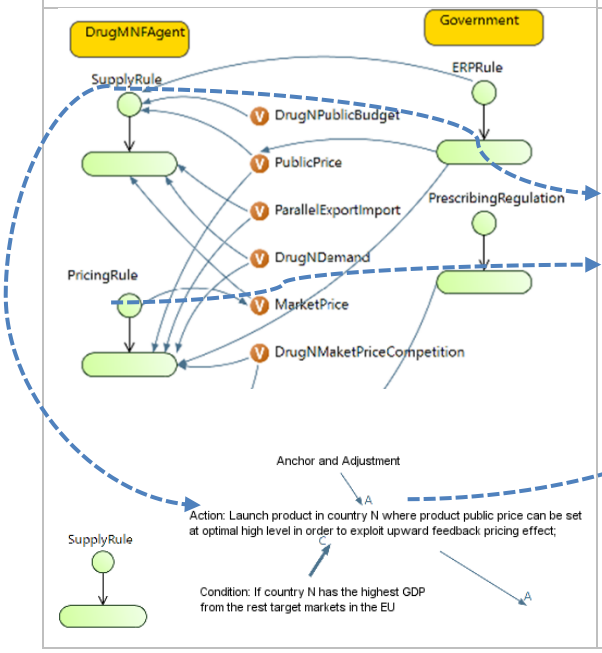
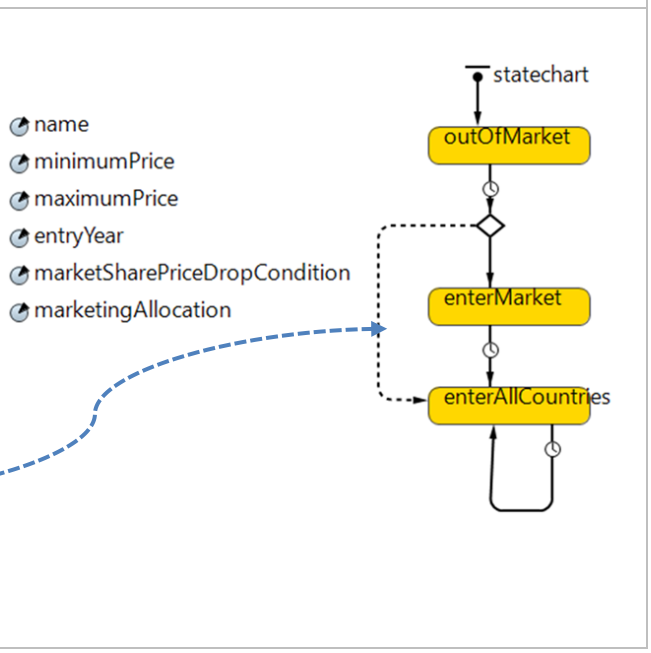
Selected elements from RAM (AiM and AbM)	Elements coded in software
	

Figure 8.6.2.1 provides illustration on the transfer of the AiM and AbM 'SupplyRule' and 'PricingRule' components into technical specification (software). Initially, a drug stays 'OutOfMarket', which at a next step enters market, after a pharmaceutical firm prioritizes its local market launch (set on GDP criterion, reflecting 'anchor and adjustment.' BDT principle). Then the drug enters all other country markets, depending on regulation conditions for local market entry and reimbursement, if there are such requirements set.

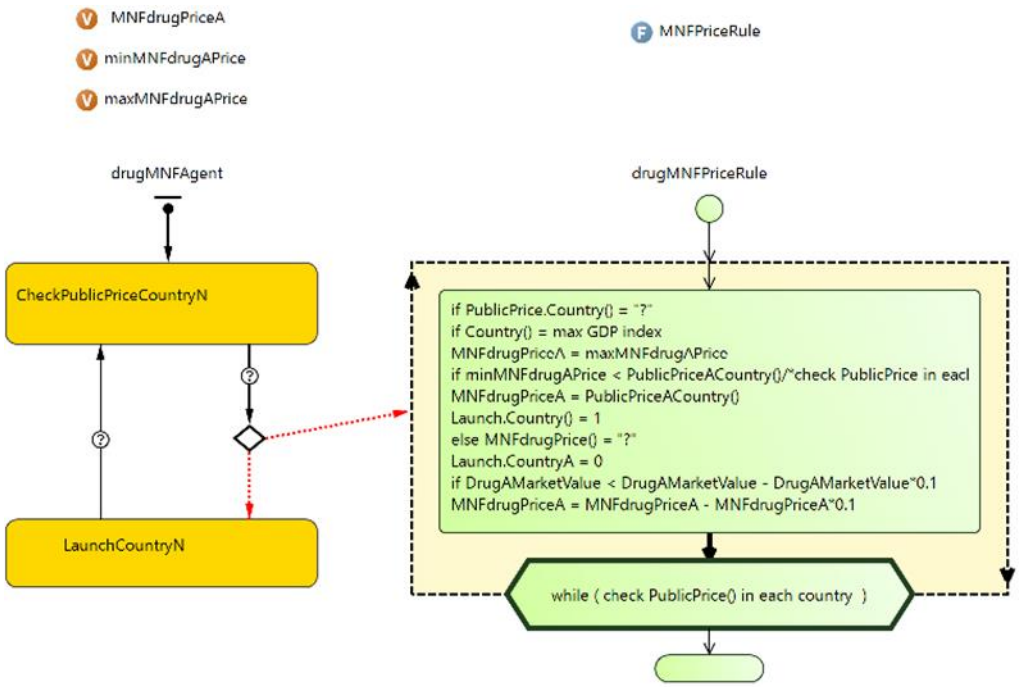


Figure 8.6.2.2 on the drafting of drug MNF agent supply and pricing rules

Before the technical software implementation of agents' charts and functions, these were explored and drafted in pseudocode for aiding their conceptualization and transfer to technical specification, bearing in mind AiM and AbM. Figure 8.6.2.2 provides illustration of this drafting and reflection stage, consisting of agent's state chart (on the left) with initial state 'CheckPublicPrice' and followuing state 'Launch', connecting agents' decision to supply with the drug SD supply chain, with decision branch in between the two states. Further, the decision to supply (to launch the drug on a chosen local country market) is elaborated in the 'Code Panel' (on the right). Anylogic software allows agents decisions for action to be coded in the form of state and action charts and in function code. The above draft version was used as a pseudocode to inform the actual coding in software.

Reading into the 'Code Panel', key agent decisions are elaborated:

- First, check drug price in reference basket countries and select countries from the GDP list
- Then, if that price is within a min to max interval, then can supply drug, else wait and check next country
- Third, if there is no drug price registered, then supply with max drug price from price interval
- Use drug price discounting range, connected to changes in market share (in value)

Table 8.6.2.3 State variables for pharmaceutical firm agents

Name	Minimum Price	Maximum Price	Entry Year	market share drop price change condition	Marketing Allocation
DrugFirmA	5	10	1	10%	10%
DrugFirmB	4	9	9	10%	10%
DrugFirmC	3	8	10	10%	10%

Pharmaceutical firm's activity states are defined in programmable code relating to the agent´s state chart and informed by the AiM and AbM (Table 8.6.2.1 presents the code for pharmaceutical firm´s agent state ´enterMarket´). Initially, a pharmaceutical firm agent is in idle state ("outOfMarket"). In year t, a pharmaceutical firm agent decides to enter a country market ("enterMarket" state), and choose country of first drug launch depending on country attractiveness, here related to the value of GDP index (a country with maximum "gdpindex" value is regarded as most attractive due to its highest purchasing power). After finding the country with maximum gdpindex, a pharmaceutical firm agent sets its drug price at a maximum value, which in turn becomes country's public price ("publicPrice"), and starts supplying its drug (sets "launch" variable to "1") to this local market. The next drugFirm agent activity state ("enterAllCountries") is connected to their entry in all available country markets at time t1, having a condition for the countries public price ("publicPrice") > min. drug price of the drug firm.

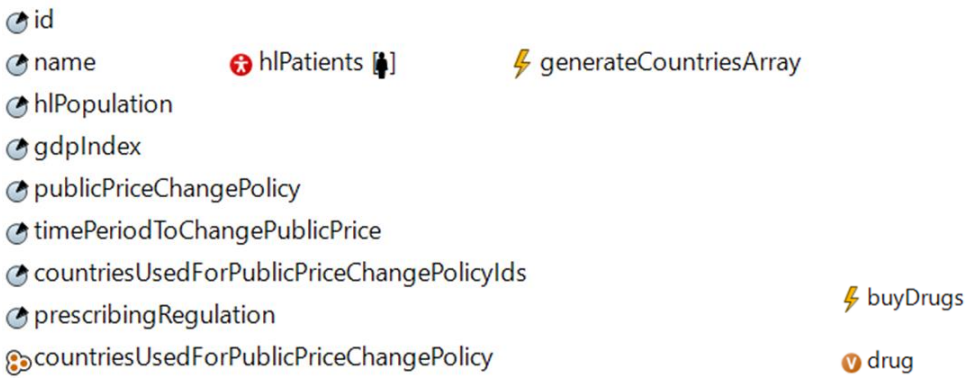
Pharmaceutical firm agents wait at least one year for their next product launch, after launching initially in the most attractive country market. This is due to the most common ERP requirement to reference public price of drugs that need to be already present on at least one local market from a given country basket. Pharmaceutical firms change their drug prices after comparing their product market share with its previous value once a year. Traders are configured initially to be not present in the simulation run (having

"FALSE" value) and can be included by the user by changing its value to "True". Patients buy their prescribed drugs in one pack once per month. Pharmaceutical firm agent with the highest marketing budget can have 80% probability of winning prescribing doctors (buying patients). Important functions are used to define in code how pharmaceutical firm agents change their drug prices ("changePrices"), depending on market share and price competition.

8.6.3 Country and patient agents (AB)

Countries where pharmaceutical firms supply their drugs are set as agents of agent type "Country", with attributes (state variables) and parameters defined in an excel sheet table (Figure 8.6.3.1 and Table 8.6.3.1).

Figure 8.6.3.1 Country and patient agents



In Table 8.6.3.1, countries number can be increased or decreased, and specific parameters can be defined to each one (analogically to drug firm's number and parameters). Each country agent has an "id" number, which is used in configuring reference country baskets for public price calculation by each country, through the parameter "countriesUsedForPublicPriceChangePolicyIds". Countries "gdpindex" parameter is used by drug firm agents for their entry decision strategy. "publicPriceChangePolicy" parameter is used for setting the reference price calculation formula to either average ("avg") or minimum ("min"), and "timePeriodToChangePublicPrice" is used for setting the reference price recalculation frequency per each country. The "prescribingRegulation" parameter defines if drugs are allocated and sold by their brand names ("brand"), triggering drug firm agents' competitive strategy by marketing budget allocation; or by their molecule name, defining pharmaceutical firm competitive strategy by drug price ("price"). By "calculatePublicPrice" function (Table 8.6.5.3), each country is looking for prices of a drug supplied by one pharmaceutical firm in different countries (included in the reference

country basket for the relevant country) and calculates average ("avg") or minimum ("min") price, according to the reference "public price formula" per country, specified in code in Table 8.6.3.1.

Next Figure 8.6.3.2 and Table 8.6.3.1 present pseudocode for government agent ERP price calculation rules.

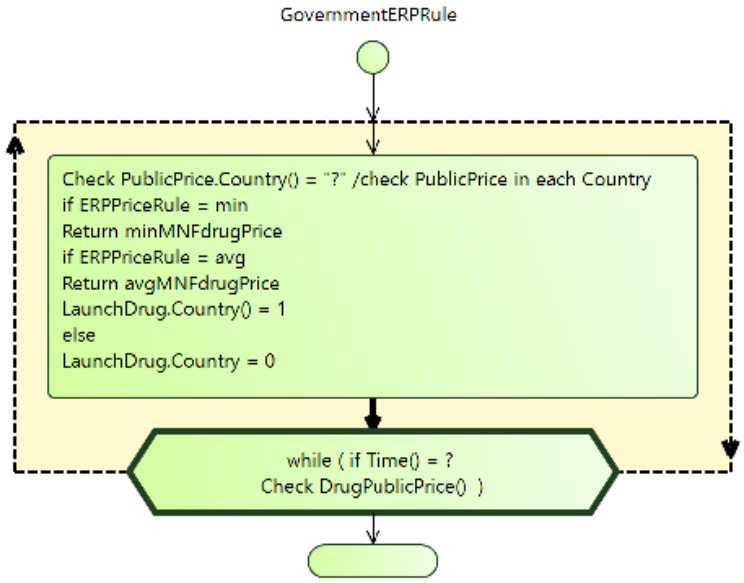


Figure 8.6.3.2 on drafting of government ERP regulation rule

Figure 8.6.3.2 consists of reflection notes on the government agent ERP rule (behavioural pattern). First, this agent checks price of same drugs in all ERP basket countries, then returns the minimum or average drug price. This check is performed once, twice or N times per year (time period for drug price revision). Discounted public prices can be checked if they are official. Government can choose to apply own price discounts.

Table 8.6.3.2 Initial state variables for each ERP country (countries are listed in the table with their international abbreviations)

Id	Name of country	HlPopulation	Gdpindex	public price formula	time period to change public price (years)	countries used for price calculation policy	prescribing regulation
1	Country AU	100	45.081	avg	1	2,5,6,7,8,9,10,11,12,13,15,16,18,19,20,21,22,23,25,26,28,29,30,31	brand
2	Country BE	100	41.57	avg	1	1,3,5,6,7,8,9,10,11,12,13,15,16,18,19,20,21,22,23,25,26,27,28,29,30,31	brand
3	Country BG	100	15.732	min	1	8,9,10,11,12,13,18,19,26,27,29,30	brand
4	Country CR	100	21.351	avg	1	1,7,8,13,23,31	price
5	Country CY	100	31.198	avg	1	1,10,13,28	brand
6	Country CZ	100	29.018	avg	3	2,8,9,10,11,12,13,14,15,16,18,19,21,23,25,26,28,29,30,31	brand
7	Country DK	100	43.782	avg			price
8	Country E	100	25.823	min	1	15,19,21	brand
9	Country FI	100	39.869	avg	5	1,2,3,5,6,8,9,10,11,13,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31	price
10	Country FR	100	37.592	avg	5	7,11,18,31	brand
11	Country GE	100	43.887	avg	1	1,2,6,8,10,11,12,13,16,18,23,26,28,30,31	price

12	Country HU	100	23.336	min	1	1,2,3,5,6,8,9,10,11,13,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31	brand
13	Country GR	100	25.667	min	0.255	1,2,3,5,6,8,9,10,11,13,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31	brand
14	Country IC	100	42.035	avg	2	8,11,25,28	brand
15	Country IR	100	45.677	avg	3	1,2,7,8,11,12,13,23,31	price
16	Country IT	100	35.075	avg	2	1,2,3,5,6,8,9,10,11,13,15,16,19,20,21,22,23,24,25,26,27,28,29,30,31	brand
17	Country LA	100	22.534	avg	2	3,6,9,15,21,25,27,29	brand
18	Country LV	100	25.715	avg	1	6,8,9,15,19,27,30	brand
19	Country LU	100	91.048	min	1	19,8,9	brand
20	Country MA	100	29.127	avg	1	5,6,9,11,15,18,19,27,29,30,31	brand
21	Country NO	100	65.640	avg	1	1,2,7,8,11,16,23,28,31	price
22	Country PL	100	23.994	avg	2	1,2,3,5,6,8,9,10,11,13,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31	price
23	Country PT	100	27.509	avg	1	11,13,30	brand
24	Country RO	100	18.972	min	5	1,2,3,6,7,10,11,15,18,19,25,30	brand

25	Country SK	100	26.497	avg	0.5	1,2,3,6,8,9,10,11,13,15,16,17,19,20,21,22,23,24,26,27,28,29,31	brand
26	Country SL	100	28.859	min	0.5	1,7,13	price
27	Country SP	100	33.092	min	1	1,2,5,7,9,10,13,16,18,20,22,23,26,29,31	price
28	Country SD	100	33.092	avg	1	28,9,8	price
29	Country SN	100	56.940	avg	3	1,7,8,13,23,31	price
30	Country NE	100	46.162	avg	0.5	1,7,13,31	price
31	Country UK	100	38.255	avg			price

Countries used in reference country baskets are generated in arrays with the following code, presented in Table 8.6.3.1 and with initial parameters presented in Table 8.6.3.2. Initial data used for the ERP country rules was obtained from Eurostat (GDP index per country), and from Vogler, S., Lepuschütz, L., et al. (2015) and Vogler et al. (2014) , including countries local legislation sources. These parameters allow for adaptation to future changes in the ERP rules, according to changes in local legislations. Patient agents having been diagnosed with for example hyperlipidemia ("hlPatients") are included in each country through the parameter "hlPopulation" in the country parameter excel table. Their buying behavior is configured initially by a pseudocode drafted on paper and then transferred into program code (Figure 8.6.3.3).

If there is drug supplied (available) in a country market, patient agents buy drugs by their brand prescription, influenced by "doctorMarketingInfluence" function and size of pharmaceutical firm marketing budget, when prescribing regulation is by brand ("brand"). When prescribing regulation is by drug molecule ("price"), with the purpose to facilitate price competition, then patients buy whichever drug is available and cheaper.

Figure 8.6.3.3 Draft picture on doctor and patient prescribing and buying rules

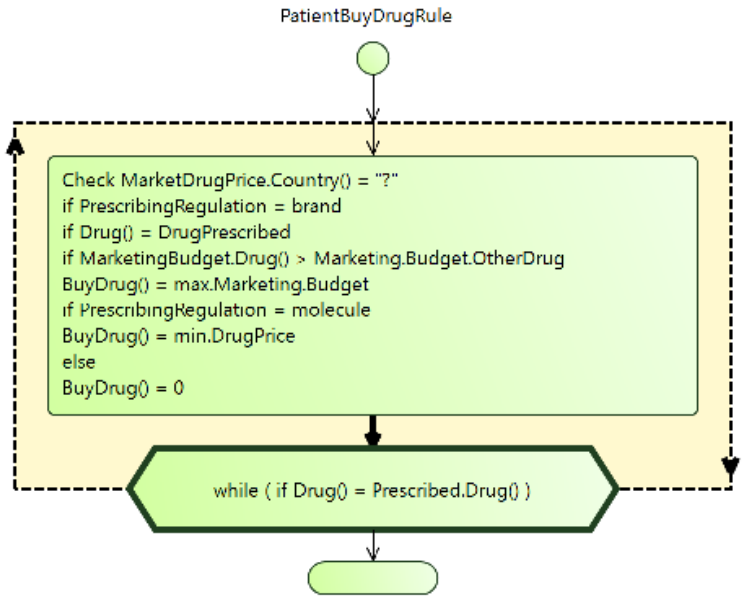


Figure 8.6.3.3 presents reflection notes on the pseudocode (rule pattern) of doctors and patients agents in the form of state charts. Doctors become prescribing agents, influenced by the rate of diagnosing patients, for example with hyperlipidemia or other cardiovascular condition. Then, they prescribe drug A, drug B or other drugs, influenced by competing drug firm agents through their marketing budgets (marketing activities).

Next, after being diagnosed, patients buy drug A, drug B or other drugs influenced by drugs price, drugs availability and marketing budget allocation of drug companies.

8.6.4 Parallel traders agents (SD and AB)

Parallel traders are included as agents ("traders") with their own parallel medicines supply chain, analogous to the supply chain of drug firm agents. Parallel trader agents have attributes (state variables) and parameters defined in Table 8.6.4.1 and Figure 8.6.4.1.

Figure 8.6.4.1

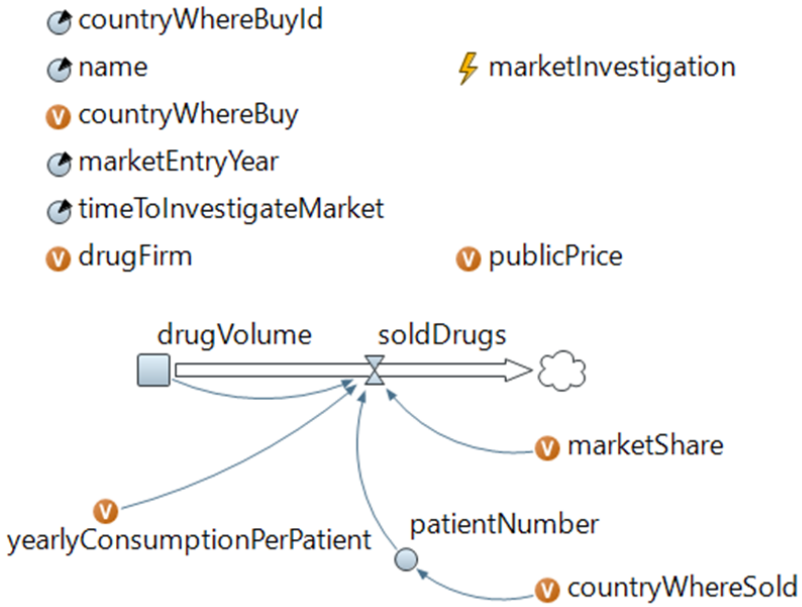


Figure 8.6.4.2 on parallel traders' action rules initial drafting

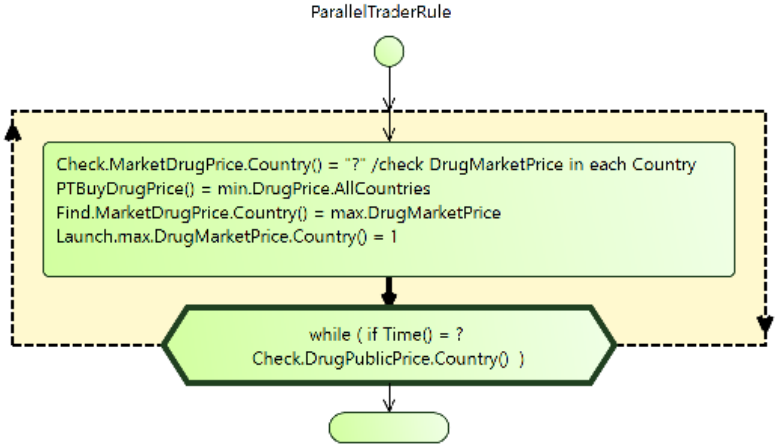


Figure 8.6.4.2 presents notes on parallel traders agents pseudocode describing their behavioural pattern. First, Parallel traders check countries' markets, comparing drugs public prices with local drug market price. If the local public drug price is the lowest among all other markets prices, then they buy the lowest priced drug and sell this drug in the market with the highest public price of the same drug, thus increasing price competition on that market.

Table 8.6.4.1 Parallel traders parameters

Name	country where they buy	Market Entry Year	time to investigate market (years)
Trader1	1	1	1
Trader2	2	1	1
TraderN	N	1	1
…	…	1	1

In each country there is at least one parallel trader agent, having "name", year of market entry and time to investigate market drug prices. Their decision to buy and supply certain drugs is configured in the "marketInvestigation" function, presented on Figure 8.6.4.2 above.

Parallel traders look for a country market where to supply, having the highest price difference between one and the same drug, compared with the country market they are located in and from where they buy. They buy a predefined random percentage,

decreasing the drug volume supplied and increasing drugs sold in their country of location. Then they calculate the selling price of the drug bought as a random function between the lowest (drug price in the country of buying) and highest price (drug price in the country of selling).

8.6.5 'Main' top level agent and presentation configuration of the hybrid simulation dashboard

The "Main" top level agent is used to provide graphical and programmable environment for all agents, their state variables, parameters and functions. This agent provides also space for plotting graphs of output variables of interest, which are made visible for the users, while performing simulation experiments.

A whole view of the simulation design cannot be presented in one place due to Anylogic software limitations. All components have been described before. Figure 8.6.5.2 in Appendix E, presents an overall view of the whole simulation structure, which can be viewed through opening each individual agents working space.

Here, main agents presented are, "drug Firms", "country Sales", "countries" and "traders". Main agents, general variables and parameters, and functions are shown on Figure 8.6.5.1 and parameters included on the 'Main' top level are presented in Table 8.6.5.1.

The Anylogic simulation design work space, project and output panel view, containing drug price evolution graphs, are exhibited on Figure 8.6.5.2, Figure 8.6.5.3 and Figure 8.6.5.4 (in Appendix E). Variables and parameters are further explained in Table 8.6.5.1.

Figure 8.6.5.1 Agents, variables and parameters, and functions exhibited in "Main" agent

There are multiple views of each agent and their graphical, functional and technical features and that's why these features have been presented and explained before coming to the 'Main' top level agent.

Figure 8.6.5.2 presents a whole view of the simulation design space of the Anylogic software and here, a view on the ERP simulation design. On the left, there are the ERP simulation project components (agents, parameters, variables, functions, SD elements, simulation presentation, 'Main' top level agent, data files and resources. In the middle, there is the view of the graphical working space for each agent and on the right, there are the technical specification properties related to each selected agent and agents' components.

Figure 8.6.5.3 provides a zoom in view of the ERP simulation project components. Agent 'country' consists of other agents like pharmaceutical firms, parallel traders, etc., presentation, parameters and variables, collections and events. Agent 'country sale' consists of similar components, including variables, functions, events and SD elements. Similarly, other agents consist of same features: 'DrugFirm', 'Person', 'Trader'. The data files include data tables for countries, pharmaceutical firms, parallel traders and general parameters. Clicking on each agent, opens that agent's working space view which can be further inspected. All agents' views have been presented and described in the previous pages. 'Main' top level agent presents a space for designing simulation output graphs and user dashboards tailored to user individual preferences (Figure 8.6.5.4 in Appendix).

Figure 8.6.5.4 provides an example of a user dashboard for the ERP simulation experimentation, containing selected number of countries and drugs prices for observation and comparison. Price evolution graphs for drugs A, B and C are included (from top left to top right) for Austria, Bulgaria, Hungary, Poland (top level), Latvia, drugs public budget expenditure for these drugs for Bulgaria, Slovakia, and drug prices for parallel traders (middle level), and drug A price evolution comparison for these six countries (lower level in the centre). On the same level, on the left side, there are included two input parameters that the user can control: 'Marketing Influence' and 'Include Parallel Trade'. Also, the user can view the number of countries, pharmaceutical firms, pharmaceutical firm supply chains ('country Sales') and parallel traders ('Traders').

Here, the order of agents activities is described in line with the three stage procedure of conceptual, functional and technical specification for the hybrid SD & AB simulation model. Since the ERP simulation model is hybrid, containing SD and AB features and elements, a three-stage procedure of conceptual specification, functional specification and technical specification is used as described in section 8 and Figure 8.3.1. The

scheduling of the agents behaviour has been carried out in the technical specification and follows from the previous conceptual and functional stages.

The order of agents actions follows the pharmaceutical market logic (as described in the conceptual specification), specifically the logic of launching new medicinal products on a local country market or a group of markets. The steps of their behaviour are as following:

1. Initially an innovative drug manufacturing agent makes a selection of the most attractive local market to launch their new on patent drug, including calculating their drugs price, according to a ranking list of ERP countries (based on GDP index attractiveness), and according to the ERP rules set by the local pricing authorities.
2. The manufacturing agent then launches their drug in the rest of the countries following the ranking list and the ERP rules of the other countries (referring to the drug price which has been already launched in the first country).
3. Drug prices are periodically (each year, or any other time period) recalculated according to the ERP rules of each country pricing authorities.
4. After 10 years of patent protection, another manufacturing agent of a rival generic drug launches their drug and one year later after the first generic drug, a second generic drug manufacturing agent launches their rival drug (all drugs contain the same active pharmaceutical ingredient).
5. Patients agents buy and consume their drug according to the prescribed scheme (one pack per month).
6. Parallel trader agents (one agent per local market) act in a random mode after waiting for at least one year, in order to compare drugs prices among different local country markets, after which they buy the cheapest drug from one local market and sell that drug onto the local market with the highest price of the same drug.

Different agents have different information, which relates to company agent specific information like maximum and minimum drug price, competitive pricing tactics (% to decrease one´s drug price due to market share competition). ERP rules for local country markets and local GDP indexes are transparent for all manufacturing agents as they are in the real market. Parallel traders agents have information on drugs public prices among all local markets, but do not have information about rival parallel traded drug price mark ups.

There are two stochastic elements in the model: (i) individual drug manufacturing agents pricing tactics (% of market price discount due to local market competition) since these are not transparent in practice and are kept as companies trade secret, and (ii) the

parallel trader agents pricing tactics (price differences between buy and sell price). These elements can be made deterministic by selecting one or another number, representing the percentage for the price discounting of the manufacturer's drug price or the percentage number for the price difference between the parallel trader's buying and selling price. The simulation can run either with or without the above stochastic variables.

Table 8.6.5.1 Parameters exhibited in "Main" agent

Parameter	value	unit	notes
time to wait for new launch	1	year	how often a company tries to launch in a new country
time period to change price	1	year	how often the drug company reviews their own price
Use Traders	FALSE	unitless	
time between drugs for patient	30	day	how often patients buy drugs
doctor marketing influence	80%	unitless	probability that a doctor will be influenced by marketing efforts

Scenario experiments are initialized with the purpose to support the setup of simulation exploration, related to the research questions. I have used real market data (regarding drugs maximum market launch price and minimum price before market withdrawal) and real ERP rules data for local country markets, including prescribing practice for CVD drugs (statins, anticoagulant and hypertensives, which are one pack per month) and local prescribing regulation (if on innovative or generic brand or on INN) or mandatory price discounting related to local market drug reimbursement regulation.

The simulation structure is initially configured to include the following number of pharmaceutical firms and their supply chains, countries and parallel traders:

- One innovative pharmaceutical firm (drugFirmA) supplying drugA
- One generic pharmaceutical firm (drugFirmB) supplying drugB
- Another generic pharmaceutical firm (drugFirmC) supplying drugC
- A supply chain for each pharmaceutical firm (three supply chains per country)
- One parallel trader per country having a parallel supply chain (31 parallel traders)
- 31 countries with 93 pharmaceutical firm supply chains

8.6.6 Hybrid simulation model verification and validation

8.6.6.1 Verification and validation approach

The hybrid simulation modelling confidence building followed main recommendations and practice from the relevant literature, connected to gaining trust in system dynamics and agent-based simulation modelling practice, summarized in a table (Table 8.6.6.1 in Appendix E).

I have taken an approach ensuring a consistent and reproducible confidence building procedure following practical applications in the field (Howick et al., 2008; Macal et al., 2014; Kim and Andersen, 2012; Djanatliev et al., 2014; Klügl 2008). These are examples, related to practical confidence building in models for multiple audiences through a 'modelling cascade' procedure, validation of an ABM simulation of electric power markets, building confidence in causal maps generated from purposive text data (explained in previous chapters 5 (section 5.1), 6 (section 6.1) and 7 (section 7.2)), and using structural and behavioural validity tests.

I have chosen to follow the above approaches because I have applied similar procedure for qualitative and quantitative modelling and simulation design. I have used purposive text data to generate causal maps and to inform the design of resource agent maps, then I have continued with the technical transfer of the RAM into a quantitative simulation which involved system dynamics and agent-based design steps and properties relevant to the Howick et al. 2008 and Macal et al. 2014 practical examples described in their papers.

In relation to the ERP focus of my PhD research, the validation framework had the purpose to build confidence from pharmaceutical system stakeholders and experts that the applied RAM modelling and simulation approach is theoretically sound and can provide conceptually and operationally true representation of market resources and agents behaviour.

First, the simulation model building followed a technical procedure of transferring the validated conceptual qualitative RAM into a technical quantitative simulation model. All the maps content (resources, agents, agents' rules and interconnections) have been proved to be an "understandable and tight description of how the "world" works" (Howick et al. 2008) since they come from documented stakeholders' statements (tables 6.1.A, 6.1.B, 6.1.C, and Figures 7.2.1, 7.2.7, 7.2.8 , 7.2.9, 8.1.1, 8.6.6.9, 8.6.6.24, 8.6.6.25, 8.6.6.26, 8.6.6.27, 8.6.6.28, 8.6.6.29), and have been regarded by stakeholders' representatives and independent experts to exhibit "legitimacy and rightness" (Franco, 2006).

The above ensured (following Heath et al. (2009)) the first requirement for a quantitative simulation building validation, related to the first stage of the conceptual validation. This is then followed by a second stage of operational validation to ensure that the simulated system behaviour corresponds to the real system behaviour. Both stages of the simulation model building must be consistent with the applied theoretical framework and the related behavioural criteria. Here they have been introduced as a support to the ´resource agent´ perspective behind the SD and AB hybridization.

The operational validation of the hybrid model followed the Ormerod and Roswell's (2009) requirement for model replication and outcome explanation, and that "behavioural rules should be capable of justification using evidence from outside the model". It also followed a ´confidence building´ requirement (Sterman, 2000) through continuing the conversation conducted with experts and stakeholders, now focused on the simulated behaviour of the modelled system and its components and their level of true representation (justification) according to Franco (2006), Mingers (2000), and Howick et. al. (2008).

Another principle of simulation modelling validation followed here is that ´the main purpose is not accurate prediction of what will occur, but instead greater learning and understanding of the causal mechanisms involved in the situation´ (Mingers, 2000).

Numerical validation and verification (if the simulation model is producing the right performance) is achieved through the following.

All equations and code in the simulation model have been checked for technical and functional adequacy throughout the whole coding and testing procedure, and edited if any errors or inconsistencies were found. Also, technical documentation has been written and included in this chapter for complete explanation of the simulation model building and coding procedure, including description of variables, parameters, values and agent rules in line with the "conceptual-functional-technical" specification procedure, which

provides better procedural means for explanation and reproducibility of the simulation modelling process than the "overview, conceptual design and detailed description" (ODD) framework as used in North and Macal (2014) and in Grimm et al., 2010. The purpose of this is to provide transparency and means for independent check and replication of the simulation modelling composition and results.

There are a lot of published research using simulation, but a few publications are related to using hybrid (SD, ABM and DE) simulation in different combinations, applied within healthcare. In my literature review on the use of hybrid SD, ABM and DE in healthcare systems six used SD and DE hybrid simulation, three used AB and DE hybrid approach and one used SD and ABM hybrid combination (Cassidy et al. 2019). This shows how little in number there are SD and ABM hybrid applications in the reviewed field.

In this respect, not all papers provided information on validation and verification approach. Out of all hybrid SD and DE, SD and ABM and ABM and DE (Cassidy et al. 2019), just three papers included account of the validation and verification approach applied.

Djanatliev (2012) and Djanatliev et al. (2014) have used structure validity through direct structure tests (conceptual confirmation test) and achieving credibility from review by experts including on data sources and assumptions used, as well as the results of the simulation. Kittipitta et al. (2016) applied behaviour validity test using simulated output compared to real data (T-test).Viana (2018) applied behaviour validity through simulated output compared to real data and reviewed by experts and structure validity through Structure-orientated behavioural tests (structure-confirmation test, extreme-condition test).

In relation to my confidence building procedure, I have ensured structure validity of the qualitative and quantitative model (RAM and scenario simulator) through using documented stakeholder assertions and subject matter experts opinion, and through performing parameter variation tests, confirming structural adequacy. I have ensured behavioural validity through comparing simulation results with real drug price historical data through visual comparison between real and simulated drug price evolution (Ormerod and Roswell, 2009; Djanatliev et al., 2014).

8.6.6.2 Comparison to official drug public price evolution data obtained from the EURIPID project, available for the period of 5 to 10 years.

This data is regularly collected from price regulation authorities of most of the EU countries for the purpose of ERP regulation. Comparing simulated public price evolution with real data for a number of drugs showed close proximity (can be viewed in Appendix E to this chapter, containing excel documents and on Figures 8.6.6.1, 8.6.6.2 , 8.6.6.3, 8.6.6.4, 8.6.6.5, 8.6.6.6, 8.6.6.8, 8.6.6.9).

On the following graphs price data are compared for on patent innovative drug ticagrelor (no generic competition), for off patent original clopidogrel and generic clopidogrel and for off patent original atorvastatin and generic atorvastatin with their simulated price evolution for drug A, drug B or drug C (drug A simulating the on patent and off patent innovative medicinal product and others simulating competing generic drugs).

Factors that influence simulated price evolution are ERP rules, market brand competition and rival price tactics, parallel trade competition and demand and local prescribing regulation on brand or on INN (drug molecule name).

Initial drug price parameters for each simulated vs real drug price comparison, differ from the actual drug price with a small fraction, in order to provide better opportunity for visual comparison. ERP rules (parameters) in the simulation experiments are the same as their real local market counterparts, and pharmaceutical firm pricing tactics related to the percentage of competitive price decreases, are derived from real price evolution data taken from EURIPID. For calibration purposes, real market drug price evolution data have been used (EURIPID drug price data): maximum drug launch price (for market launch) and minimum drug price (before market withdrawal), including real local country market ERP rules (reference country basket, time period for drug price recalculation, referencing to min. or average drug price and other), according to Vogler et al.(2015).

Graph 8.6.6.1 Comparison between real and simulated drug prices: on patent Ticagrelor in BG v on patent drug A.

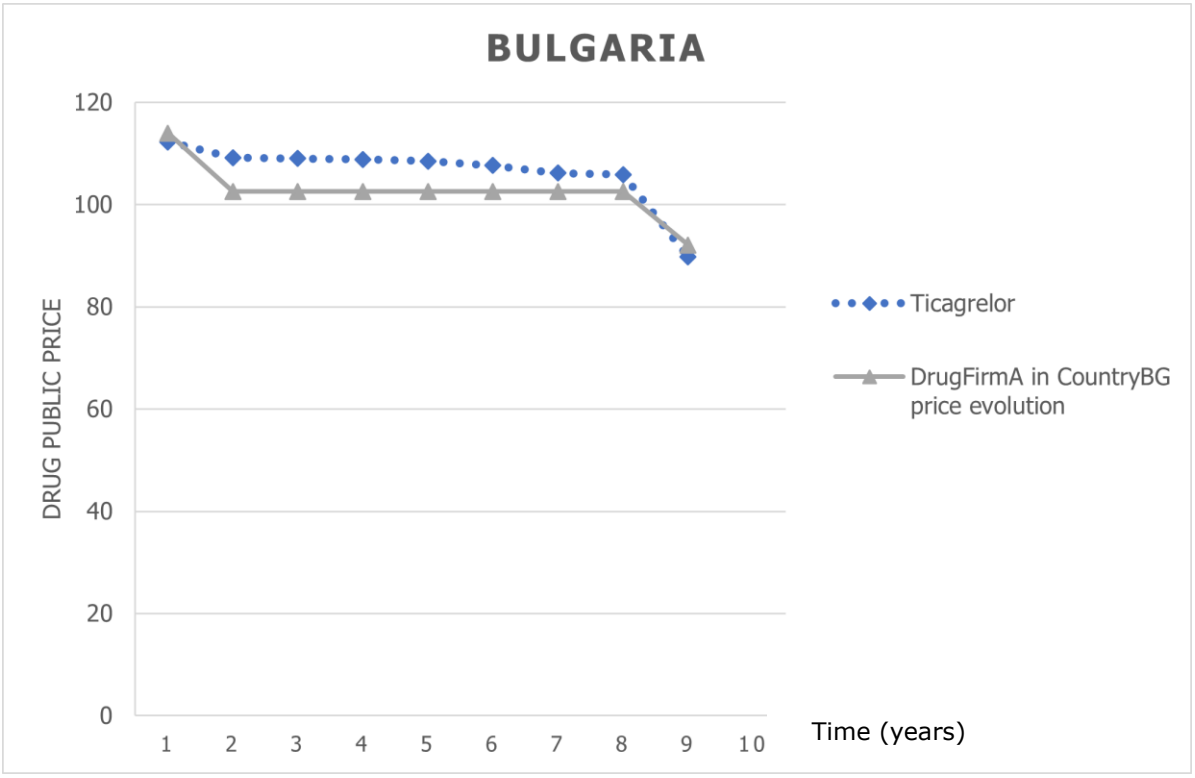


Figure 8.6.6.1 Comparing drug price data for real vs simulated (Drug A) on patent brand Ticagrelor (price per pack in Bulgaria, BGN)

Source of real data: MoH Commission on pricing and reimbursement, link: www.ncpr.bg

A visual comparison test performed on the two compared drug price evolution data (on patent real drug Ticagrelor 90 mg vs on patent simulated drug A) showed no difference between the two.

Figure 8.6.6.1 and Figure 8.6.6.2 above present comparison between real and simulated drug price data for a CVD innovative on patent drug Ticagrelor. Price data for Bulgaria was adjusted to local registered prices per pack (reported on the following web site: www.ncpr.bg), while drug data for other countries are reported per drug daily dose DDD in the EURIPID data. ERP rules, implemented for all countries in the simulation are 'mimicking' those that were relevant to each country at the time they have been reported in Vogler et al. (2014). Drug price data are taken from Bulgarian price regulator at the MoH, available at the following link: www.ncpr.bg. Drug price data for other compared countries are taken from the EURIPID database (Agreement NEAK MFF 40113/2021).

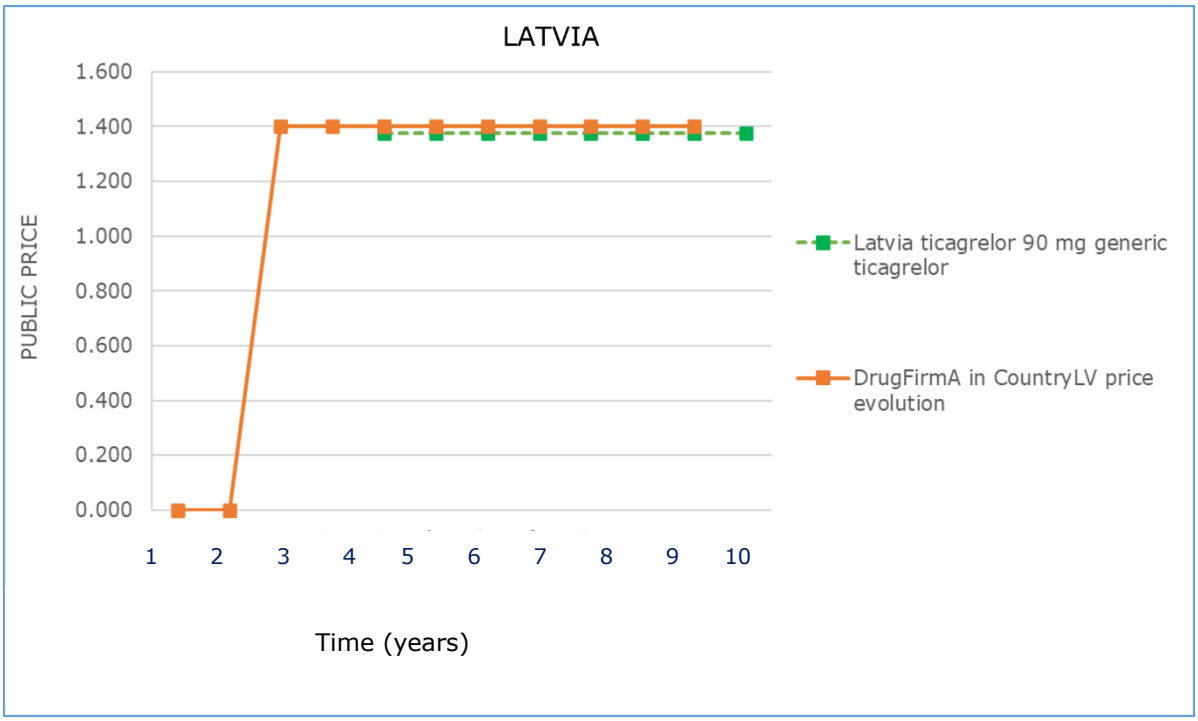


Figure 8.6.6.2 Comparison between real and simulated drug prices: on patent Ticagrelor and on patent drug A in Latvia.

Source of real data: EURIPID, price per drug daily doze (DDD)

These two examples provide evidence for validation of the simulated drug price performance replicating real drug price behaviour for on patent drugs which have a monopolistic market position and price tactic. In Bulgaria there are additional rules for state price discounts after drug launch on the local market, in order for the medicine to get reimbursement. That explains the initial price discount observed in the beginning after drug launch, while the next price decrease happens just before patent expiration and the launching of generic drug competitors. The behaviour of real and simulated drug prices almost coincides (no statistical significance in variance) in numerical comparison and fully replicates real behavioural price pattern (Ghaffarzadegan et al. 2011 p.p. 29 and 30), demonstrated through the two different examples for Bulgaria and Latvia. In Latvia, price evolution of Ticagrelor remains unchanged because there are no price decreasing requirements like state discounting or other. Simulated price of drug A for Latvia mimics the real drug price trajectory in full, providing evidence for the capabilities of the simulation to reproduce different behaviour of one and the same on patent drug in different countries, through the period of patent protection.

Graphs 8.6.6.3 and 8.6.6.4 (in Appendix E) provide real data for price evolution of on patent CVD drugs Ticagrelor 90 mg and Alirocumab 75 mg in other EU countries like AU, Belgium, Cyprus, Estonia, Finland, Greece, Italy, Portugal and other (EURIPID data). That

data provide evidence for drug prices of on patent drugs behaviour following the two main patterns described above: either maintaining unchanged price levels or changing initially due to state price discounting. The second price changing beaviour is transferred to other ERP countries either in the same or similar pattern or gradually due the local ERP price calculation formulas which take min or avg prices from ERP countries local baskets. These on patent drug price patterns are reflected in the simulation output on graph 8.6.6.3 (in Appendix E). They show that on patent drugs follow similar evolution pattern among ERP countries with little difference in countries where there are state mandatory price discounts usually initially once or twice, which can spill over to referencing countries.

The same pattern for Ticagrelor 90 mg applies also to other on patent cardiovascular drug Alirocumab 75 mg (Figure 8.6.6.4, Appendix E). This innovative drug, having again no competition, follows an evolution of either no price decrease or once or twice decreasing due to both or either state discounting and ERP spillover effects among ERP basket countries. There are also differences in the time of local market entry of one and the same drug which could result from prior country presence requirements or other regulation factors like delay in the local price registration procedure.

Comparing these graphs (Figure 8.6.6.3 and Figure 8.6.6.4 in Appendix E) with simulated on patent drug prices (Figure 8.6.6.5 in Appendix E), clear close similarity can be observed between real and simulated "patterns" of price evolution. Three pattern types are distinguished: no change in price, change in price through state discounts and gradual change in price due to price calculation set up in the local ERP rules on ‘average’. These three types of patterns are captured in the simulated price behaviour on graph 8.6.6.5.

"Pattern" comparison can further strengthen confidence generation in the simulation conceptual, functional and technical validity to provide "accurate" Ghaffarzadegan et al. 2011 p.p. 29 and 30) means for ERP evaluation. Another observation of real and simulated price behaviour provides also similar effects connected to timing of drug launch. Delays of one year of drug launch are observed both on real and simulated graphs, which could result from requirement for min number of countries presence of the drug before local price and reimbursement registration and for marketing authorization approval.

On Graph 8.6.6.6 drug price evolution of clopidogrel (original and generic brands) are compared with simulated price evolution of drug A, drug B and drug C, "mimicking" real drug products behaviour. Simulated results provide evidence for a close proximity to real ‘pattern’ of the drug price behavior.

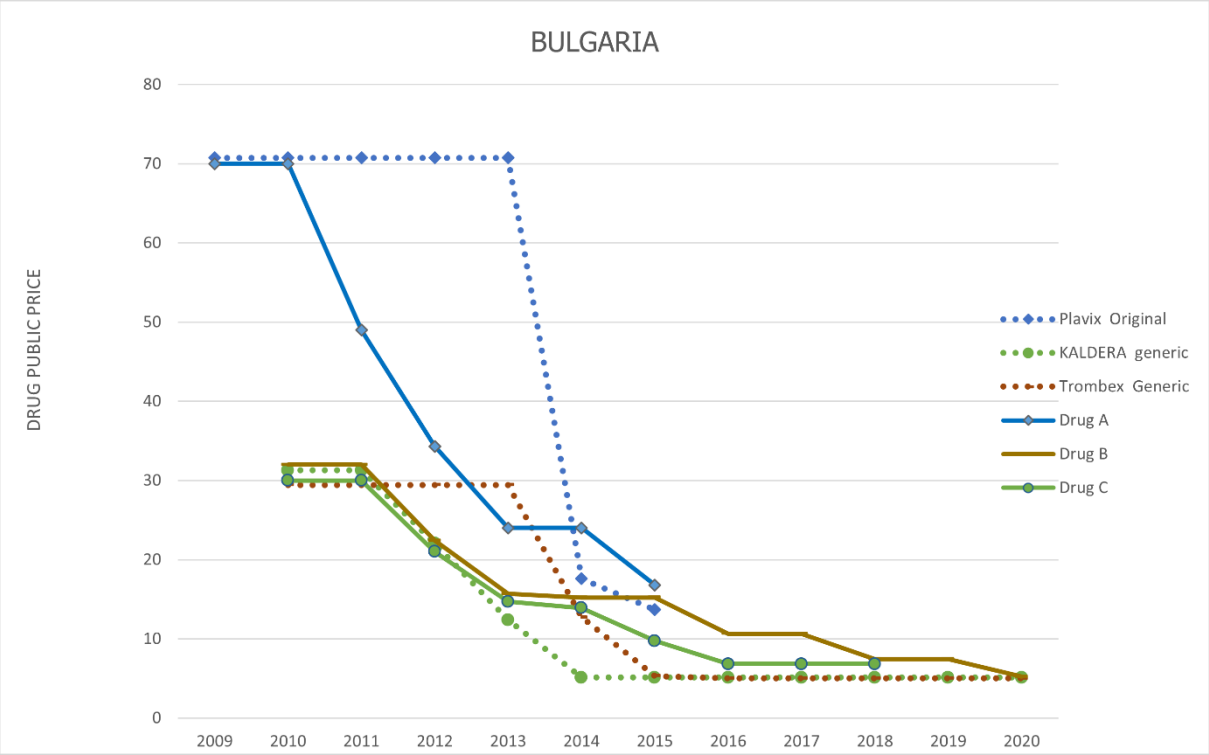


Figure 8.6.6.6 Comparison between real and simulated (Drug A, Drug B, Drug C) drug price data: original brand clopidogrel (Plavix) and generic brands (Kaldera, Trombex) in Bulgaria.

Source of real data: MoH Commission on pricing and reimbursement, link: www.ncpr.bg

Visual comparison tests performed for real and simulated drug price evolution for Plavix (on patent original drug brand), Kaldera (generic drug brand) and Trombex (generic drug brand rival) vs drug A (on patent drug), drug B (first generic drug) and drug C (next generic drug), have proved no statistical differences between each pair of real and simulated drug price evolution data.

After maintaining high price levels during on patent no competition period, even in the presence of ERP, original clopidogrel starts quickly to reduce price due to the price competition of entering generic drugs, until deregistered from the local market five years after generic rivals launch (Figure 8.6.6.1). Simulated price of the innovative drug A follows the same pattern. The prices of real and simulated generic drugs also follow close

evolution, providing further evidence for simulation confidence. Performed visual comparisons proved no statistical differences between compared drug price evolution data.

Next Figure 8.6.6. (results on clopidogrel comparative drug price evolution in Austria), provide further confidence in the simulation conceptual and functional capabilities to produce simulated drug price evolution behaviour following real drug price data at close levels, without statistical difference.

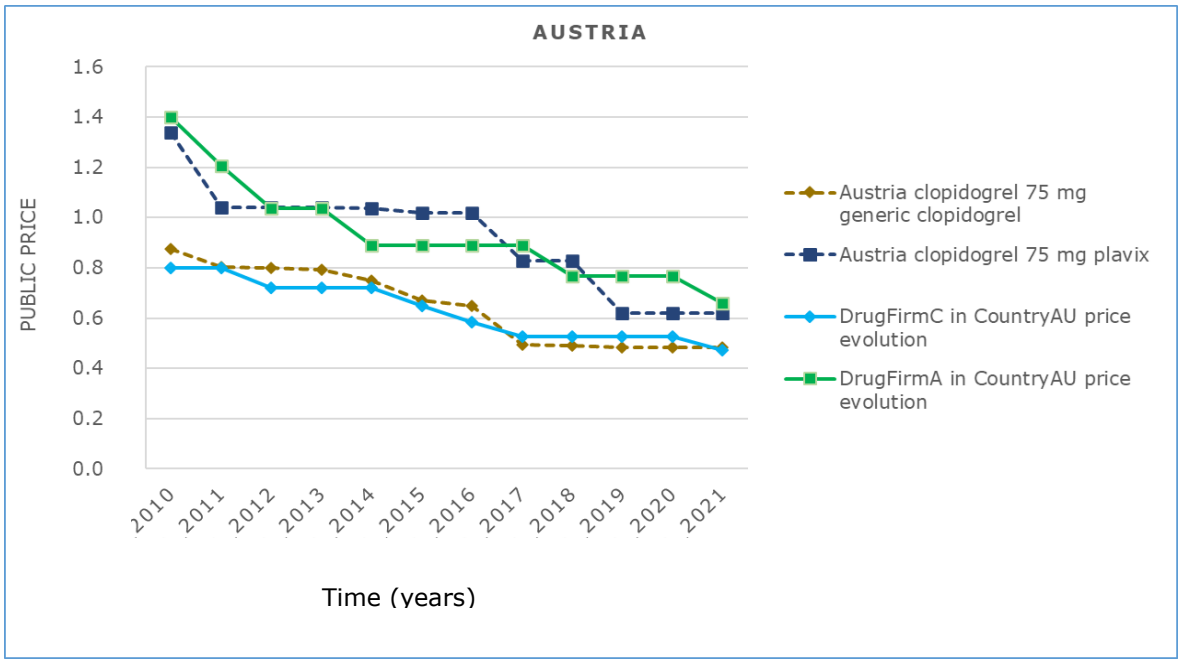


Figure 8.6.6. Comparison between real and simulated (Drug A and Drug C) drug price data: original and generic brands clopidogrel 75 mg in Austria.

Source of drug price data: EURIPID

This provides better condition to compare drug price real v simulated evolutions on 'price to price' and on 'pattern to pattern' comparative approaches.

On all graphs, which exhibit real and simulated drug price evolution, initial Simulated drug prices have been set up to start from the point of entry of real drugs prices at a close level with the purpose to make the comparison and price evolution observation easier.

Next graphs 8.6.6.8 and 8.6.6.9 provide further evidence for simulation validation and confidence through comparison of real and simulated price evolution of another cardiovascular drug treating high levels of cholesterol: Atorvastatin original and generic brands in Bulgaria and Austria.

Here, again drug price sources are different (national pricing commission for Bulgaria and EURIPID data for Austria), which provide further evidence for confidence generation in simulated behaviour.

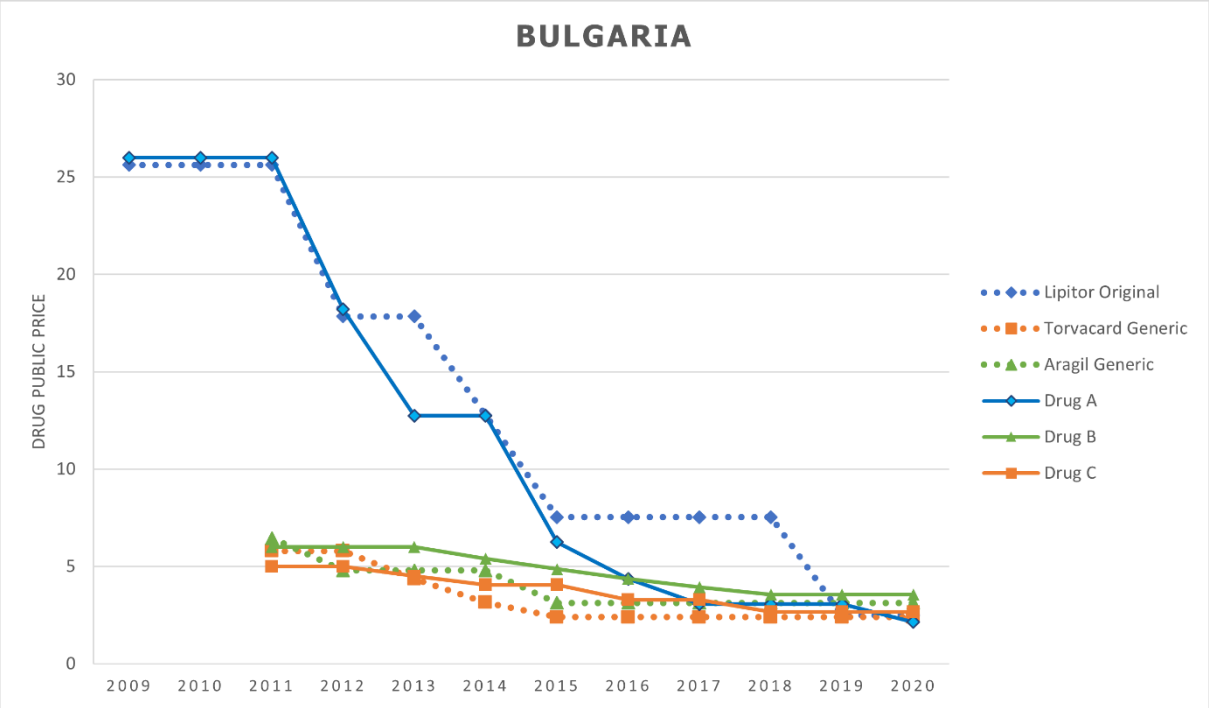


Figure 8.6.6.8 Comparison between real and simulated (Drug A, B and C) drug prices: original Atorvastatin brand (Lipitor) and generic brands (Torvacard and Aragil) in Bulgaria.

Source: Bulgarian Pricing Commission, price per pack.

Visual comparison tests performed on real and simulated drug price data, once again showed no statistical differences between compared pairs or drug prices evolution for Torvacard (generic), Aragil (generic) and Lipitor (original off patent) drug brands.

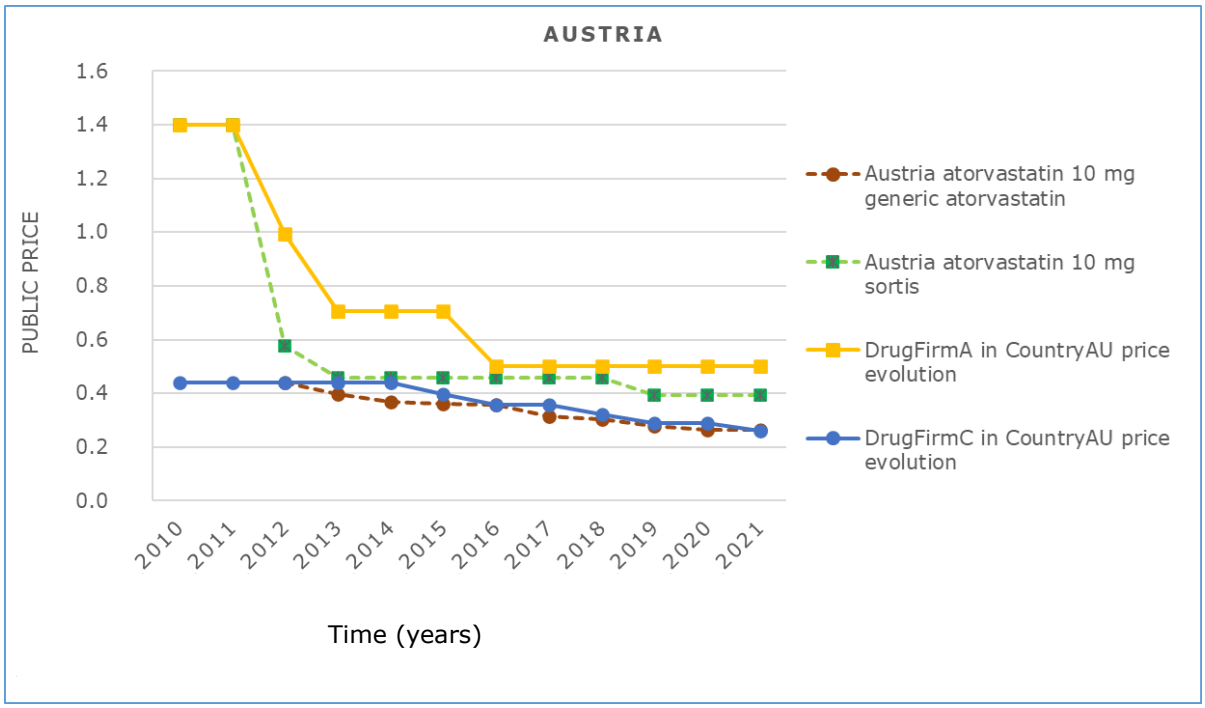


Figure 8.6.6.9 Comparison between real and simulated drug prices: original Atorvastatin brand (Lipitor) and generic brand in Austria.

Source: EURIPID, price per drug daily doze (DDD)

Simulated price evolution follows very close proximity with real drug price evolution (Figure 8.6.6.9) and fully mimics real price pattern of change in time period observed, shown in the previous four graphs (Clopidogrel and Atorvastatin) and including the behaviour of on patent drug prices. This ensures that the ERP scenario simulator is configured to "realistically" and "accurately" (Ghaffarzadegan et al. 2011) represent real market price behaviour, providing confidence in the simulator correct configuration in terms of ERP rules setting, pharmaceutical firm price tactics and market competitive rules, demand and supply market structure and relevant functional and technical components.

All of the presented examples of comparison between real and simulated data on original on patent, original off patent and generic drug prices, have been compared for existence of statistical differences between real and simulated price evolution through visual comparison.

These tests (Gilbert et. al. 2018) provide further confidence in and validation of the simulation design conceptual, functional and technical "accuracy" (Ghaffarzadegan et al. 2011) to represent correctly (conceptually and numerically) the ERP regulation effects on market system behaviour.

Figure 8.6.6.10 and Figure 8.6.6.11 in Appendix E provide a comparative "pattern" (Ghaffarzadegan et al. 2011) behaviour of real and simulated drag prices of original and generic clopidogrel 75 mg in selected EU countries like Austria, Bulgaria, Greece, Latvia, Poland, Slovakia.

They clearly show one and the same "pattern" of declining prices for both original and generic drugs after patent expiry of the innovative drug and the entering of generic drug rivals, which marks a starting point for market price competition, interfering with ERP regulation local rules. Also, the simulated "pattern" of drug price evolution captures delays in local market drug launches, and drug market withdrawals.

A number of drug price evolution graphs per ERP countries, with calculated "trend lines" (MS Excel) are selected to support drug price evolution "pattern" analysis. Real drug price data are taken from the Euripid data base.

First three graphs (provided in Appendix E) provide drug price real data with trend lines for Slovakia, Latvia and Poland for Atorvastatin 10 mg and Clopidogrel 75 mg original off patent brand and generic rival brand (Figure 8.6.6.12 to Figure 8.6.6.14). Next come drug price graphs for the same drugs in Austria, Hungary, Cyprus, Finland, Greece (Figure 8.6.6.15 to Figure 8.6.6.19).

What appears common for almost all countries, innovative drug prices which become off patent decrease quicker than their generic drug rivals due to competition effect since the entering of generic drugs to a local market marks the starting point of this price decrease of their off patent original reference products having the same INN molecule. This competition effect interferes with the ERP regulation of each ERP local market which transfers price levels among referenced ERP basket countries.

Another interesting point that can be made is that in some country’s prices of same drugs decrease quicker than in other countries, which could be due to different competition intensity levels, noticeable in countries having INN prescribing opposed to other with innovative or generic brand. In some countries the original off patent drug exit the local market some years after generic drugs entry to that market like in Slovakia and Poland.

Comparing trend lines for drug price evolution in ERP countries with simulated drug price data can generate evidence for the following. Drug price evolution pattern, according to the ‘trend lines’ in the presented figures, appears the same for all countries with a difference among local markets with INN prescribing regulation (Slovakia and Poland etc.), where pharmaceutical firms compete on price rather than on brand marketing, compared with countries with "brand" prescribing regulation (Latvia, Austria, Bulgaria),

where companies compete on marketing budgets. In first group of countries with INN (MOLECULE NAME) prescribing, drug prices tend to decrease quicker in comparison with the second group of countries with prescribing on innovative or generic brand.

This contextual effect is further explored in the ERP simulation experiments in chapter 9, showing that the evaluation results of the ERP regulation in Bulgaria exhibit the same 'pattern' of drug price evolution for innovative original drugs (on patent or off patent) and for generic rival drugs provided in the EURIPID drug price data (Figures 8.6.6.11 to 8,6.6.19 in Appendix E). This provides logical reason to consider the ERP evaluation results for Bulgaria valid and that these results can further be applied analogically also to the ERP effect in other ERP countries.

8.6.6.3 Conducting meetings and conversations with experts

ERP simulation scenarios were shown to pharmaceutical market experts from Bulgaria and EU (industry experts, price regulation authority experts, independent experts), who agreed to participate and to have their opinion used anonymously. This was conducted through in person and online meetings. All experts were shown same output and were asked the same questions (Appendix E). All experts gave their opinion on the ERP regulation effects and their relevance in connection to the ERP simulation design and results, and agreed with having confidence in the simulated performance output and "pattern" behaviour, regarding the ERP effect on market system behavior (Table 8.6.6.9 in Appendix E), including parameter values assumptions related to agents behavioural routines configuration.

Figure 8.6.6.20 in Appendix E provides copies of documents regarding working with experts involved in the Medicines for Europe task force on ERP regulation and Euripid guide on the topic. Figure 8.6.6.21 and Figure 8.6.6.22 provide examples of an email for scheduling a meeting with Medicines Industry Association in Brussels and a document containing meeting notes with subject experts. Also, the ERP qualitative map (RAM) and quantitative simulation results were presented and discussed during working group meetings on the COST Action EU initiative on medicines shortages.

Out of the researchers notes from first and follow up meetings and conversations with the above association in their Brussels offices, interesting and informative questions have emerged, which further provided support to the elaboration of the resource and agent maps.

For example, while conducting these interviews and conversations questions about who will be using that simulation model And how, to whose benefit, provided accent on the purpose of the ERP evaluation to support public policy decision making and on the dichotomy between pharmaceutical companies and public policy makers perspectives; Further, the interviewees put accent on the importance of main unwanted effects of the ERP regulation (if a medicine is withdrawn) and their appropriate communication with public policy makers, using simulation scenarios accounting for this effect.

The discussion on what prices were made public drew attention on the issue of whether market price discounts are taken into account within the ERP public price calculation, and informed further what if simulation experimentation scenarios. A focus was put on parallel traders effect on supply volumes of drugs and put importance on the role of parallel traders and the need of their inclusion in the simulation. Further, the interviewees acknowledged the importance of competition effects on drug prices and the need of consideration of competition within the simulation analysis.

Also, an online meeting with a member of the Euripid project and coauthor of the Euripid guidance report was conducted. This expert used the DE Simulation from the EU commissioned project on ERP evaluation (Toumi et al. 2014) to produce a research paper on evaluating the effects of variating selected ERP rules in one chosen local market. This simulation was limited to evaluating only ERP effects connected to obligatory public price discounting, excluding parallel trade effects and pricing and marketing tactics of drug companies, and consumers behaviour. Also, neither verification nor validation support has been officially provided for this DE simulation, which leaves not enough reason for confidence in the DE simulation design, functions and results. However, a number of attempts have been made also to conduct a call with another user of the DE on the topic, but that user denied at the end to be interviewed and to provide expert opinion.

All conversations with subject matter experts and industry associations reiterated main themes, already included in official documents on the ERP topic and evident in the document analysis done in the qualitative RAM stage. Figure 8.6.6.24 provides main quotes from documented statements on the ERP regulation effect on the markets in EU.

Figure 8.6.6.23 Main quotes from documented statements on ERP regulation effects and their document sources

Official publication	External Reference Pricing /ERP/ Effect on pharmaceutical market and agent activity
1. Toumi et al., 2014	○ different scenarios illustrated spill-over and circular effects of ERP; ○ support previous studies on industry's incentives to engage into launch sequence strategy; ○ Further researches to include parallel trade into the model could make this tool even more powerful; ○ other pricing policies, potentially amplified by ERP /INN at doctor, Co-payment, pharmacy regulation/
2. EGA/EFPIA	○ EGA: referencing prices in countries where procurement and tendering systems are in place (driving down the prices to unsustainable levels) would be detrimental for the Gx, for patients (availability of affordable Gx) and for payers (savings); ○ EFPIA: ERP and parallel trade created spill-over effects from low price to higher price countries leading to patient access issues in low price markets
3. Leopold et al.	○ apply strategic pricing methods when launching products; ○ industry and insurance institutions reach lower prices through discounts/rebates
4. Carone et al.	○ industry negotiates discounts with distributors /not communicated/ and leave listed prices unaffected. Pay-back mechanisms may ex-post lower the effective prices, parallel trade may lower effective prices in high price countries. Packaging also differs; ○ industry may adapt strategically and continuously to ERP, partially eroding the potential for cost-containment. The industry can launch products in countries with high pharmaceutical prices first (e.g. Germany); ○ industry may avoid competition on prices and rather competes on discounts; ○ ERP may lead to prices being too high /price inflation/ and not reflecting national market conditions;
5. Wouters, O.J. et al. (2013)	○ manufacturers apply launch strategies to exert upward pressure on prices (e.g. launch delays or product withdrawals); ○ EPR is associated with important short- and long-term issues

All experts have been asked to observe the performance of each scenario experimentation and to give their opinion on the simulated results and if they can regard them to be a true (´right and legitimate´ according to Franco, 2006, ´justifiable´, according to Ormerod and Roswell's (2009)) representation of real behaviour (´how the world works´, Howick et al., 2008)

Comments that have been received by the experts were positive in respect to the main question of a true representativeness of the simulated results (provided on previous pages). They included expert's opinion on price evolution, drug companies' behaviour, ERP regulation effects and experiments' parameter setting. In the next Table 8.6.6.9 (in Appendix E), main quotes showing ERP experts opinion, are provided.

Multiple simulation runs with parameter variation have been done to test consistency of the simulated output with documented real market behavior observations and published research (Appendix E to this chapter on published info on drug price behaviour and on EURIPID drug price data evolution). Simulated results and comparison with real drug price data are provided here and ERP simulation experimentation results are provided in the next chapter 9). More than that, counterintuitive behaviour has been explained by contextual market and contextual regulatory effects, coming out mainly of the variation in prescribing regulation, reference country baskets and parallel traders' activity on local market (provided in the next chapter 9 on ERP regulation experimentation). The above parameter variation proved that the hybrid simulation approach applied is capable of capturing real complex market behaviour and produce insights for its analysis and explanation.

8.7 Discussion

8.7.2 Capabilities related to the ERP hybrid simulation model and its functions

The hybrid simulation model is capable of including all EU and EEA countries applying ERP or being part of reference country baskets. It is also capable of including higher or lower number of drug supplying agents (varying drug supply and competition level) and drug demand agents (varying demand level).

The number of parameters included, provided opportunity for calibration with real market data (drug prices, ERP calculation formula and reference country basket configuration, pharmaceutical firm and drug trader agent's number, their marketing and competition strategies, etc.)

The simulation model can be further configured to provide opportunity for high number of parameter variation runs, Monte Carlo, in software calibration and or optimization, but are dependent on using professional AnyLogic version.

8.7.3 Insights gained from the ERP hybrid simulation building procedure

Main insights from the simulation scenario experiments are presented in the next chapter, while in this chapter main learning from the simulation building procedure is included.

While hybrid SD and AB simulation model building is challenging due to the lack of relevant theoretical frameworks and technical procedures (Phelan, 1999, Scholl, H.J., 2001, Ackermann et. al., 2014), here a new approach is applied, aiming to fill that need, related to the following stages:

I. Conceptual simulation model building

This stage was greatly supported by the application of the RAM tool, which provided a qualitative conceptual modelling procedure for the functional specification of the quantitative model: what are the modelled system components, their interrelations and behavioural rules, key variables and parameters.

Using RAM as a conceptual hybridization procedure also addresses the challenges for combination of different simulation methods like SD and ABM (Ackermann et. al., 2014). RAM use as a procedure also ensured achieving validation and confidence requirements, allowing for maintaining a very close connection and mutual reference between both, conceptual and operational stages.

II. Operational simulation model building

This stage followed after the functional specification to transfer its requirements related to the modelled system components and behaviour to a technical (programmable in software) setting, ensuring a consistent match between the qualitative and the quantitative representation of the simulated system.

In practice there are challenges connected to the technical integration of the SD and the AB simulation due to the differences and incompatibility in the software applications associated with the two simulation paradigms. However, using Anylogic can overcome this challenge as it provides a single software environment that is capable to support simultaneous SD and AB simulation model charting and coding, including iterative performance testing.

RAM can be used for a theoretical framework, conceptual reference, scenario generation and testing, expert opinion reference, and as a tool for ensuring and supporting

confidence and validation requirements. This supported the application of a consistent approach for SD and AB hybrid simulation (both qualitative and quantitative) and addressed a need in the theory and practice of multimethod approaches.

In this stage, RAM helped in the technical integration between SD and AB coding (structural interconnections and behavioral rules), since the combined resource agent map contained all the needed qualitative data related to the hybrid modelling design, SD resource (stock and flow) structure and agents rule pattern, including interactions among SD and AB components. The RAM provided a clear and comprehensive view on resource structure and resource flows and agents decisions, and how they are interconnected.

8.7.1 Limitations related to the ERP hybrid modelling and simulation configuration

The ERP hybrid simulation model has technical limitations related to the maximum number of system dynamics components and agents that can be used due to restrictions in AnyLogic versions applied (PLE or AnyLogic University). For this reason, the simulated experiments were conducted with less number of agents (one innovative drug and two generic drug companies, which supply to 31 EU countries (93 drug supply chains in total, with 31 parallel traders and limited number of consumers in each country). The simulation results showed that having the right conceptual, functional and technical specification can produce credible results even when the simulation design is simpler rather than more complex (Ghaffarzadegan et al. 2011). There are also deliberate limitations on variables and parameters number introduced in order to provide opportunity for tractable analysis of scenario experimentations, related to the simulation modelling focus on ERP effect on drug access, availability and affordability. Further, in a more complex model, more parameters and variables, related to resources and agents' attributes can be included if other research questions become part of the model scope and boundary.

8.7.4 Limitations related to the software used

AnyLogic software does not allow for a big (whole) picture view (contemplation) of the connections between all agents, resources, variables and parameters. Instead all components can be inspected in their separate work space view (page) in the software project windows. This is specifically relevant to the agents' interactions between

themselves and with systems resource structure and components. While one can have a view on the SD components in one window, and on each agent characteristics (parameters, variables, functions and state charts) in another, this cannot provide an immediate observation of the interrelations between all these components of the system structural and functional design. This is why the integration between SD stocks and flows (including their mathematical representation) and agents behavioural rule functions (including their programmable code) need to be carefully configured with iterative observation and testing of the simulated system performance. The above limitation is an important challenge, which was approached by the use of the hybrid qualitative RAM. The RAM helped not only as a hybridization procedure to ERP simulation and confidence building, but also as a tool for maintaining a whole picture and "comprehensive" reference view of the whole modelled system and associated components and interconnections.

Chapter 9 ERP Regulation Simulation Analysis and Policy Recommendation

9.1 Introduction

The simulation analysis of the ERP regulation presented here, comes as a second step of the hybrid resource agent qualitative and quantitative modelling framework for the evaluation of the ERP effects on equitable drug access, affordability and availability in the EU countries.

The simulation design and analysis follows the RAM qualitative model of ERP regulation and applies it as a hybrid quantitative simulation building procedure, described in Kazakov et al. (2021).

The procedure of transferring the RAM of the ERP to a simulation model is described in the previous chapter, including confidence building steps through theory led thematic analysis of purposive text (Hayes 1997, Kim and Andersen, 2012), conversational approach (Mingers and Rosenhead, 2004; Franco 2006) with three groups of experts, and comparison of simulated output in connection to drug price evolution (Macal et al., 2014) to real public prices in a number of EU countries.

The analysis of the ERP regulation, presents a number of what if scenarios, conceptualized through the RAM approach and performed through the use of a public policy scenario simulator. They have the task to elicit the effects of the ERP tool box and

its elements in combination with important contextual regulatory and market competition factors (Table 9.1.1). It extends further the practice of public policy evaluation through simulation, bringing a comprehensive approach (Rosenhead, 2006), building upon and combining the following two principle perspectives related to system dynamics and agent-based modelling and simulation applications to the topic:

- How small system dynamics models can help the public policy decision making and evaluation process (Ghaffarzadegan et al., 2011)
- Computational Modelling for evaluation of Public Policy: Reflections on Practice (Gilbert et al., 2018)

The principles of the above two perspectives applied here, are related to the practice of simulation models to provide interactive learning environments, where modelers and policy makers can design and test policies through experimentation and gaming (Ghaffarzadegan et al., 2011).

Using simulation helps to illustrate why intendedly rational policies can lead to policy resistance and can support the design and testing of robust policies, accounting for the counterintuitive nature of policy problems. Also, simulations can help to build consensus and can allow policymakers to explore how behaviours are created endogenously, through a broad model boundary. In relation to policy evaluation, simulations can provide means for comparing behaviour 'patterns' between simulated and real data and an apparatus for 'accurate' representation of the simulated real systems (Ghaffarzadegan et al. 2011 p. 29 and 30).

Policy evaluation can be performed through developing a computational model and running simulations with and without implementation of a policy, and then compare formally the two model outcomes with each other and with reality (with the policy implemented), using quantitative analysis through multiple simulations, sensitivity analysis, and 'what if' tests (Gilbert et al., 2018).

This allows for the exploration of alternative interventions and policy options, simply by trying out numerous parameter variations, and experimenting with context-specific scenarios along different horizons. Such simulation modelling experiments enable recursive learning by stakeholders, who can achieve system competence and practical skills through testing different scenarios and learn 'by doing' how to manage complex situations.

9.2 RAM scenario setting

ERP hybrid simulation experimentation is set with connection to the following scenarios (Table 9.2.1), related to the scenarios generated using the qualitative RAM analysis in chapter 7.

The purpose of the scenario setting and experimentation is to examine the effects of what if changes in the ERP regulation components, together with contextual changes related to local price regulation (having effect on local market price competition) and parallel trade activity (having effect on supply and price competition across country markets). This will ensure that the ERP regulation effects will be analyzed not as an isolated mechanism but interfering with important contextual price regulatory and market competition factors locally and across EU ERP markets.

On Figure 9.2.1 a graphical user dashboard example is provided showing main important input parameters and chosen output variables. Such user dashboards are an easy way for decision makers to configure what if experiments and observe results. Main input parameters used in the scenario experiments included in Table 9.2.1 are:

1. Changes in price calculation formula
2. Reference countries basket variation
3. Time period for price revisions and recalculation
4. Local prescribing regulation variation, and
5. Parallel trade competition.

In all presented scenarios, parallel traders and local prescribing regulation are taken as a controlling factor for comparing output indicators. Here in this example of a user dashboard, such output observable variables are product launch time, price evolution over a simulated time horizon, product market exit time, public budget spending and prices of parallel traded drugs, connected to drug access, affordability and availability criteria.

The input and output variables above have been selected according to the following criteria:

- Input variables need to present options for varying the ERP tool set, connected to price calculation formula (calculating min or avg value of a drugs price in reference countries basket), reference countries basket (changing selected countries for price benchmarking and their number), time period for price revision

(how often a drugs price is benchmarked and recalculated), contextual factors of importance like parallel trade competition and prescribing regulation

- Output variables need to provide options to observe ERP effects related to the research question criteria of equitable access, affordability and availability of medicinal products (launch time, price evolution, market exit, public budget expenditure)

Scenario simulation experiments are set to explore uncertainties connected to the degree to which the ERP rules can capture drug prices' competitive market discounts, that are resulting from the drug manufacturing agents' pricing tactics for decreasing their drugs' prices due to market competition, and the parallel traders pricing. In this respect, the hybrid simulation model is 'not stochastic' in principle, because all the parameters for ERP rules and drug launch strategies are deterministic, including the drug manufacturers' and parallel traders pricing tactics (percentage decrease or increase in the drug´s price). These pricing tactic related parameters are made stochastic in the uncertainty experiments, which involve 100 runs with stochastic variations within minimum and maximum percentage intervals related to the abovementioned elements (Section 9.3.10).

Figure 9.2.1 Customized user dashboard example for ERP scenario setting and simulation experimentation, connected to the research question of evaluating ERP regulation effects on equitable drug access, affordability and availability criteria

The Figure 9.2.1 presented here, exhibits four output graphs. The first graph on the upper left provides a window for observing drugs local market time of access and drugs price evolution over time (affordability level) and drug market exits. The next graph to the right, exhibits public budget expenditure including out of pocket payments associated with each drug sales volume through the observed simulated time period. The third graph to the right exhibits drugs prices of local parallel traders and which countries they are exporting to. The fourth graph below the previous three, exhibits comparative price evolution of the same three drugs in six chosen countries: Austria, Bulgaria, Poland, Latvia, Hungary and Slovakia.

These countries were selected because they have suitable features for the purpose of comparison of drug price evolution. These include, available data, reference baskets, GDP and drug prescribing regulation. All the graphs provide users with options for selecting a variable of interest reducing the graphical output to focus on that variable.

The following table (Table 9.2.1) provides an overview of the scenarios selected for testing and simulation experimentation. These scenarios have been conceptualized through the use of the RAM qualitative problem structuring approach, described in chapter 7. The scenarios generated and analysed through the RAM are explored further here, containing their main parameters, related to the variation of the ERP tool set (drug price calculation formula, reference countries, price revisions), parallel traders and local prescribing regulation effects.

The purpose of this scenario setting is to provide what if scenario situations for experimentation with changing important ERP-related input parameters and contextual factors, like the ones described above. This will provide an interactive simulation environment where ERP-related effects can be observed and evaluated against the main criteria of drugs access, availability and affordability. Some of the what if scenarios are connected to global (EU wide) ERP tool box and contextual factors variation, while other what if scenarios are experiments with ERP and contextual factors variation on a local market scale.

The quantitative simulation scenarios (Table 9.2.1) were performed to follow the logic of the simulation modelling structure and to reflect the qualitative scenarios (Table 7.4.1), which have been generated using the RAM approach.

Table 9.2.1 Scenarios setting (selected scenarios)

Scenario	Notes	Main goal
1. ERP regulation effect in EU EEA countries, matching actual ERP parameters a. Without parallel trade b. With parallel trade	This is the initial scenario, in which reference country baskets, price calculation formula and time period for price recalculation match real parameters per country; In addition, prescribing regulation and GDP per country also are included with real parameter values; It is informed by scenario III (Table 7.4.1)	Compare "ERP with parallel trade" v 'ERP without parallel trade" ' to explore what are the effects of parallel trade on an ERP global market Include analysis of the concept of price convergence due to the ERP effects
2. ERP regulation eliminated for all EU countries (no ERP) a. Without parallel trade b. With parallel trade	This scenario is an what if policy experiment, in which ERP is eliminated and price evolution would be subject to local competition and prescribing regulation effects; It is informed by scenario III (Table 7.4.1)	Compare "No ERP with parallel trade" v 'No ERP without parallel trade' to explore the effects of parallel trade on an ERP free global market
3. ERP regulation eliminated only in Bulgaria (local prescribing by innovative or generic brand) a. Without parallel trade b. With parallel trade	This scenario is aimed at testing the effect of no ERP policy, while prescribing regulation remains as it is (prescribing by innovative or generic brand); It is informed by scenario III, V and VI (Table 7.4.1)	Compare "No ERP with parallel trade" v 'No ERP without parallel trade' to explore the effects of parallel trade on an ERP free local market; Compare with scenario 1
4. No ERP in Bulgaria, prescribing by molecule	This scenario is the same as above, but prescribing	Compare "No ERP with parallel trade" v 'No

a. Without parallel trade b. With parallel trade	regulation is changed to prescribing by molecule; The aim is to test the effect of a market driven by price competition as opposed to the previous scenario, where the market is driven by brand marketing budgets; It is informed by scenario III, V and VI (Table 7.4.1)	ERP without parallel trade' when local prescribing is changed from "brand" to "molecule", to explore the interfering effects of local prescribing regulation on an ERP free local market
5. ERP in Bulgaria with variation in reference country basket, prescribing by brand a. Without parallel trade b. With parallel trade	The aim of this scenario is to test ERP effect if certain countries are excluded from the price reference basket and compare it with an ERP scenario like it is in practice; It is informed by scenario III, IV, V and VI (Table 7.4.1)	Compare ERP variation effects of changes in reference country basket, and influence of local parallel trade competition and specific prescribing regulation
6. ERP in Bulgaria with state public price discount for the innovative drug at market launch and parallel trade	The aim of this scenario is to test how state price discounts interfere with ERP and their effect on the on patent drug market; It is informed by scenario VIII (Table 7.4.1)	Exploring effects of public price discounting for innovative drugs at point of market entry and influence of local parallel trade competition in an ERP local market
7. ERP in Bulgaria like above with further generic drug price competition with taking account of market price discounts	The same scenario as above exhibiting effects of generic competition interfering with ERP; It is informed by scenario II and IV (Table 7.4.1)	Exploring effects of public price discounting for innovative drugs at point of market entry and influence of local parallel trade and generic drugs

		competition in an ERP local market, when ERP regulation can capture market price discounts
8. ERP v No ERP in Bulgaria with real public drug price data and with the assumption that the ERP can take account of market price discounts	This scenario has the goal to evaluate the ERP effects when prices are benchmarked to official public price without taking into account market price discounts; It is informed by scenario I, II, III, V, VI and VIII (Table 7.4.1)	Exploring effects of no public price discounting for innovative drugs at point of market entry and influence of local parallel trade and generic drugs competition in an ERP local market, when ERP regulation cannot capture market price discounts
Simulation experiments		
9. ERP in Bulgaria parameter variation experiment (Min or avg price calculation, innovative or generic brand or molecule prescribing, price revision period)	The goal of the parameter variation experiment is to test the level of dependence of the drug price behaviour and price evolution on ERP price calculation formula, on ERP price revision time and on local prescribing regulation and on their combinations; It is informed by scenario IV (Table 7.4.1)	Compare ERP effects through parameter variations in the context and influence of local parallel trade competition and specific prescribing regulation
10. ERP in Bulgaria drug price discount uncertainty analysis experiment combined with main	This scenario consists of one hundred runs for each parameter combination experiment, testing for uncertainty in the degree of	Compare different what if scenarios This is simulation experiment 9,

	parameter variations from the previous experiment	a drug's market price discount reflected in the ERP public price; It is informed by scenario IV and VIII (Table 7.4.1)	reperformed to include uncertainty analysis and comparison of statistical mean values within 95% confidence interval;

The simulation dashboard can be configured to exhibit output graphs for each European country implementing ERP regulation and or being a part of a reference country basket, this way showing how changes in one country ERP regulation can affect drug price evolution in other ERP reference basket countries. The setting of the actual ERP regulation parameters per each country is aligned with published data in a survey on ERP practice in Europe (Vogler, S., Lepuschütz, L., et al., 2015) and shown in the chapter on simulation technical specification.

The simulation model has been tested with real public price data for all EU countries taken from the EURIPID data project and compared to public price evolution for strengthening the user confidence in its capabilities to provide a trustful representation of the pharmaceutical market public price behaviour in conditions of active ERP regulation, market competition and contextual prescribing regulation. Also, real public price testing for Bulgaria has been performed, including three different medicines for cardiovascular diseases like hypertension, antiplatelet and cholesterol treatment. For the purpose of scenario analysis, a limited number of 6 countries are chosen for graphical presentation of drug prices evolution: Bulgaria, Austria, Hungary, Poland, Slovakia, Lithuania. The selection criteria were related to the actual availability of historical reference price data, used by ERP countries, obtained from the EURIPID project data. Although the actual data obtained is limited for a group of drugs and their minimum prices, and for its time period available, it is presenting opportunity for comparison between actual price evolution and simulated price evolution, and for strengthening confidence in the capability of the simulation model to explain ERP variation combined with contextual regulation and competition effects (interference with prescribing regulation and pharmaceutical firms marketing and pricing strategies) on drug access, affordability and availability.

9.3 ERP analysis through scenario simulation experimentation

9.3.1 Scenario I: ERP regulation in EU matching actual country parameters, with and without parallel traders

To evaluate the influence of parallel traders on the system, experiment with and without parallel trader agents are compared (Figure 9.3.1.1, Figure 9.3.1.2 and Figure 9.3.1.3). The results present that parallel traders are an important factor which have effect on pharmaceutical firms competitive (marketing allocation and price decrease) strategy, even with limited number of parallel trading agents (one per country, trading with only one drug, making 31 traders among all ERP countries). The most significant effect is on the price evolution of the traded drug (usually the drug with highest price difference between country of export and country of import).

In a 'parallel trade' scenario, drug A and drug C prices remain higher than in a 'no parallel trade' scenario. This can be observed in Hungary (Figure 9.3.1.3), although one could expect this to be on the opposite, following drug price evolution in the other ERP countries. In Austria, drug C is lower in a 'parallel trade' scenario, compared to a 'no parallel trade' one, but just on the opposite, drug B becomes higher in a 'parallel trade' scenario (Figure 9.3.1.2). In Bulgaria, 'parallel trade' v 'no parallel trade' scenarios produce not only differences in drug exits number and time, but also differences in the price evolution of drug C, which is higher in a 'no parallel trade' scenario (Figures 9.3.1.1).

If parallel traders are not active, prices of some of the drugs remain higher for longer periods of time (Figure 9.3.1.1) like in Austria and Bulgaria for drug C. For example, the highest priced drug in AU and BG (drugC) remains with its price constant in the 'no parallel trade' scenario, while its price is experiencing reduction in the 'parallel trade' scenario due to the price and market share competition effects of the parallel traded drugs across local markets. As a conclusion, simulating ERP effect on pharmaceutical market without including Parallel Trade, could produce limited and misleading results, when assessing ERP effects against main criteria of equitable access, affordability and availability of medicinal products. This would also be valid for not taking into account the local prescribing regulation and pharmaceutical companies pricing and competition tactic. Their effects on the actors behaviour and on the ERP system will be presented in the scenarios to follow.

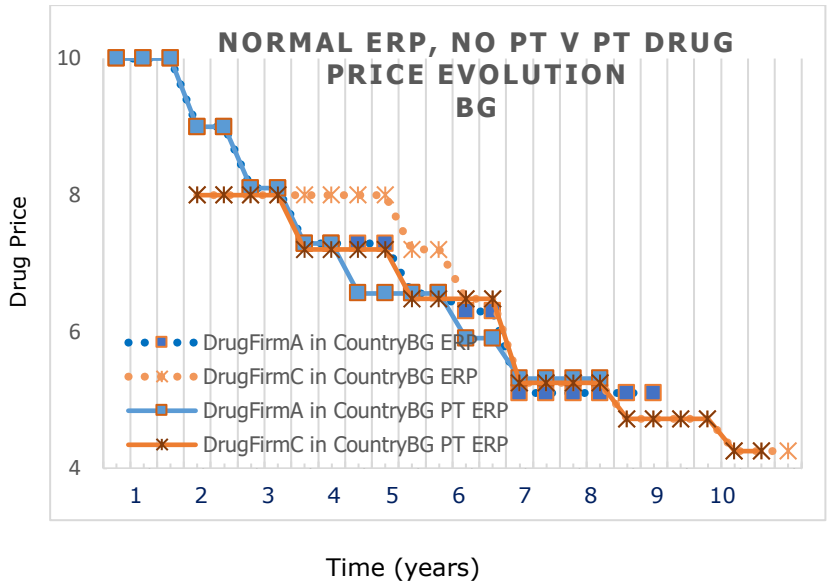


Figure 9.3.1.1 ERP Scenario I.a. "No Parallel Trade" v Scenario I.b. "With Parallel Trade" for Bulgaria, showing differences in drug C and drug A

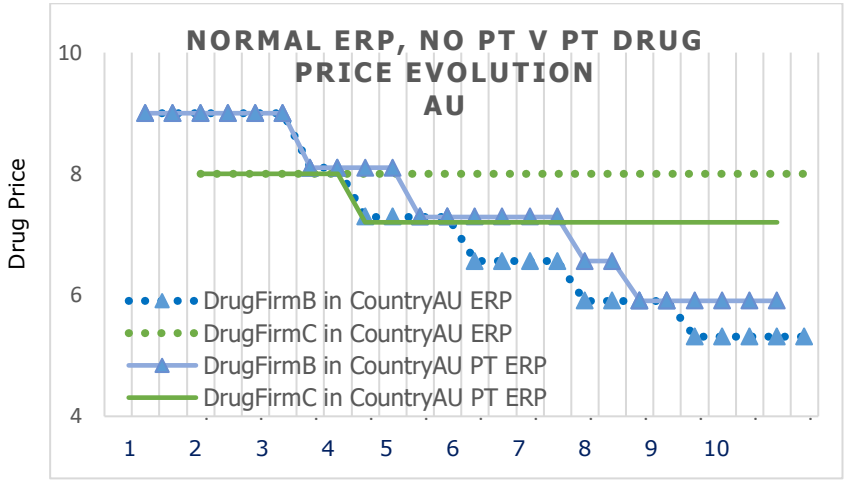


Figure 9.3.1.2 ERP Scenario I.a. "No parallel trade" v I.b. " With parallel trade" for Austria, showing differences in drug B and drug C

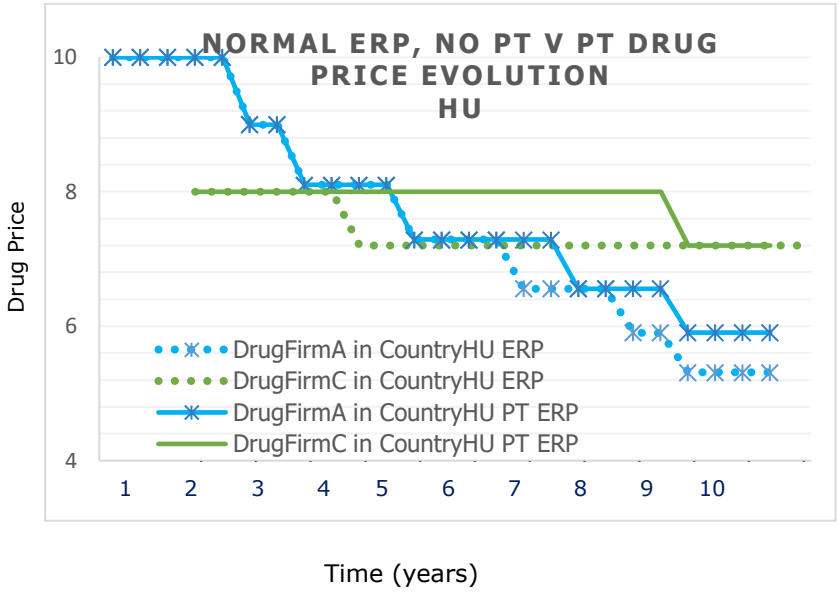


Figure 9.3.1.3 ERP Scenario I.a. "No parallel trade" v I.b. " With parallel trade" for Hungary, showing differences in price evolutions of drug A and drug C

9.3.1.1 Analysis of "price convergence due to ERP regulation" concept

Another counterintuitive outcome is related to the concept that the ERP regulation must have convergence effect on drug prices around ERP using countries (Vogler et al. 2015), while the simulation shows no evidence for converging drug prices, but just on the opposite.

Price evolutions of drug A, B and C, exhibited on Figures 9.3.1.4, 9.3.1.5, 9.3.1.6 (in Appendix F) show that even each drug is set to enter all markets at one and the same price value, during the whole simulated time period differences appear with lowest drug prices for Bulgaria and Slovakia, middle level prices for Poland and Latvia and highest level prices for Austrian and Hungarian markets. This should be due to the fact that the ERP regulation rules do not "act" in isolation. Instead, there are contextual effects (market share and drug price competition, prescribing regulation and other), that interfere with the ERP rules, and could hinder, amplify or produce counterintuitive outcomes, like those described above.

However, it could be acknowledged that certain convergence of prices could occur among ERP countries which refer to each other. This raises further questions about the reference price baskets composition and suitability in regard to achieving more equitable and at the

same time affordable price levels. An important remark should be made here, regarding the price benchmarking method and if it should be adjusted to local price purchasing parity levels, since one drug price could be regarded affordable in one country but in another it could be at a higher or at a lower level when adjusting for the local PPP criterion (Figures 9.3.1.4, 9.3.1.5, 9.3.1.6 in Appendix FX)

9.3.2 Scenario II: If ERP is not applied in all ERP countries

Figure 9.3.2.1 Comparing drug price evolution for Scenario II.a. "no ERP without PT" vs. II.b. 'no ERP with PT' scenario for drug A in Austria and Hungary

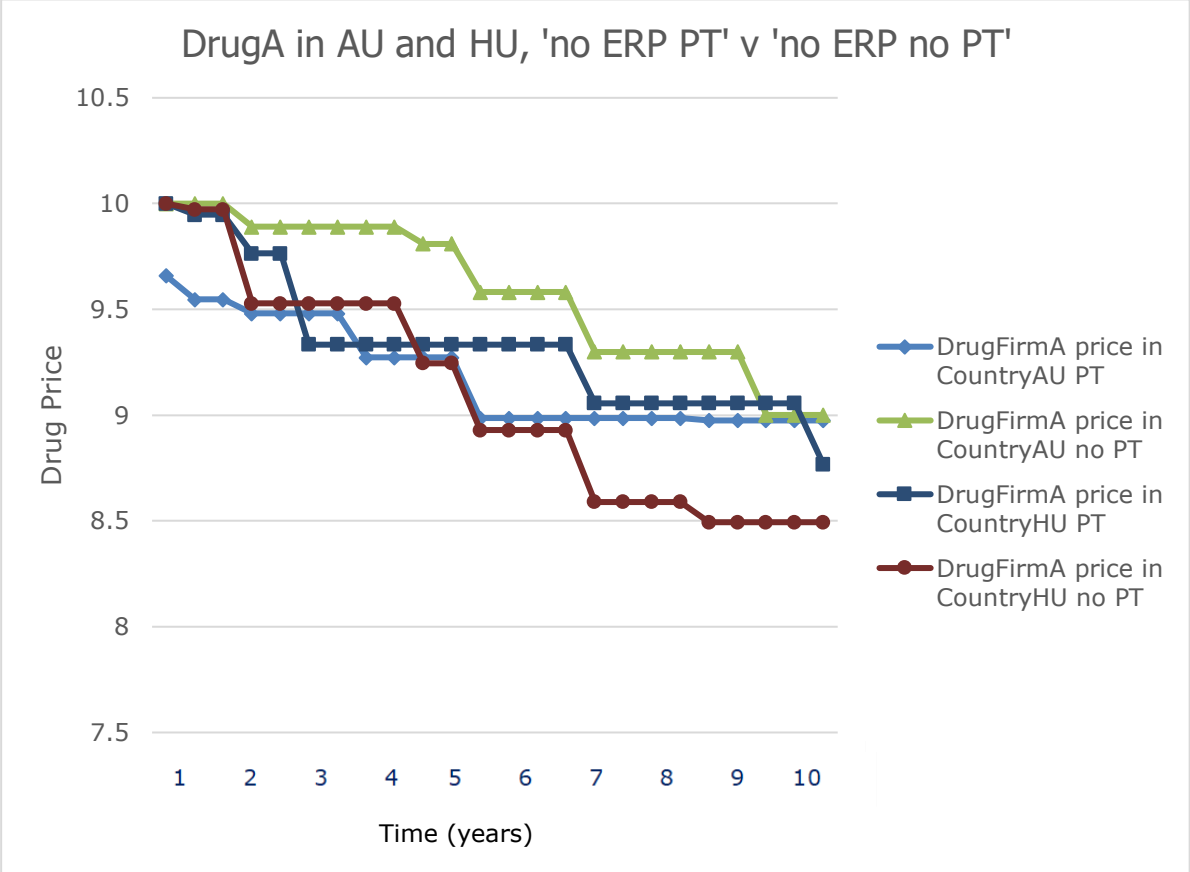
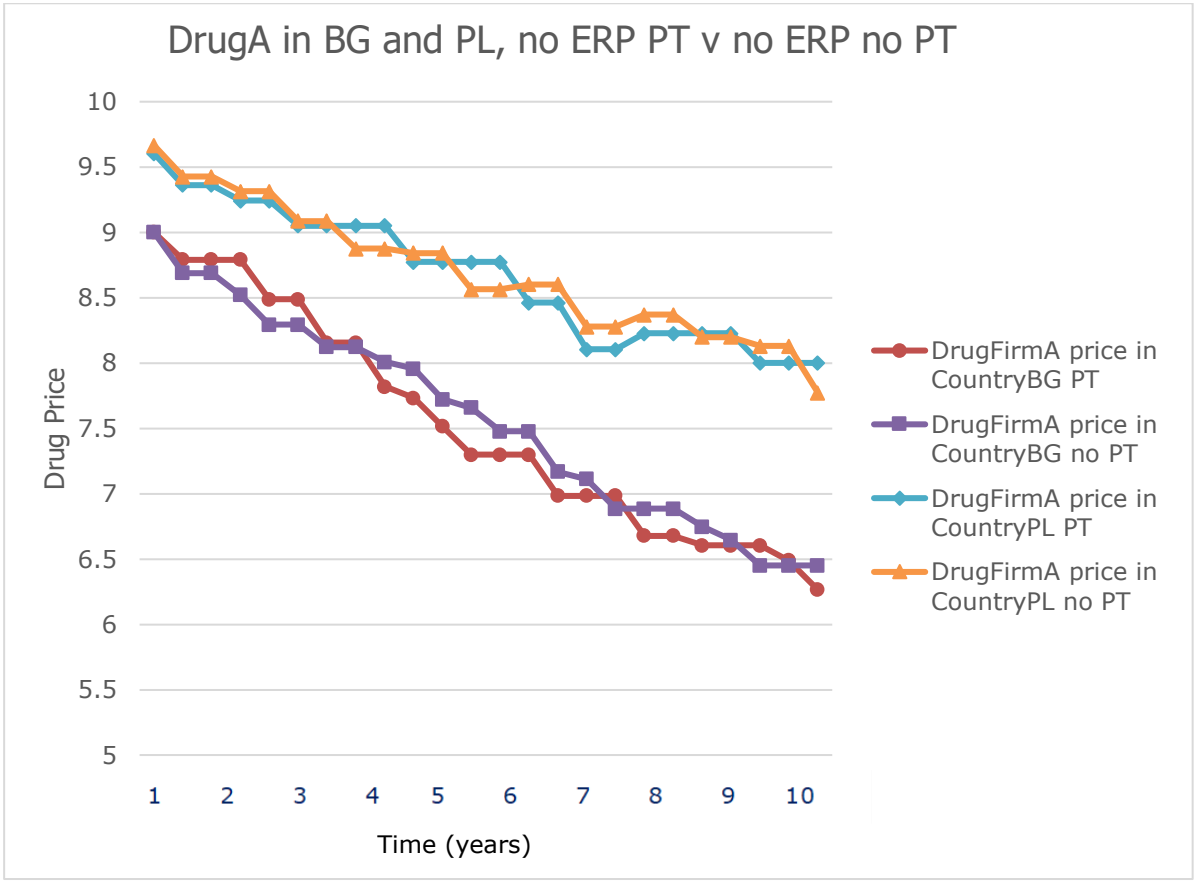


Figure 9.3.2.2 Comparing drug price evolution for Scenario II.a. "no ERP without PT" vs. Scenario II.b. 'no ERP with PT' scenario for drug A in Bulgaria and Poland



This scenario is testing the application of a 'no ERP' scenario without and with parallel trade. In this scenario, the price evolution is depending on price competition effect among all market agents supplying a given drug (drug manufacturers and parallel traders) on a local market.

Price evolution will also be dependent on contextual local prescribing regulation, which could be either by innovative or generic brand or by molecule and which is influencing the buying behaviour of consumers. Prescribing by brand usually means that patients buy drugs by their brand, and that drug manufacturers compete on marketing budgets allocated for doctor adoption, without having incentive to decrease their drug price. If prescribing is by molecule, patients usually buy more affordable (cheaper) drugs and pharmaceutical firms compete on mostly on price, which increase further price competition intensity and can lead to faster price decrease.

If there are no parallel traders in this scenario, originator drug prices remain higher for longer period of time in countries like Austria and Hungary, but if included then prices decrease faster (Figure 9.3.2.1) due to the competition effect of parallel traders' activity on drug prices and on drug market share of each drug company agent. A counterintuitive effect that can be observed in this scenario is that in certain countries (BG, PL) prices for the originator drugs decrease similarly in both PT vs. no PT scenarios, Figure 9.3.2.2, but no drug market exits occur.

These differences between the two group of compared countries could be explained by differences in contextual effects related to local prescribing regulation (fostering or not further competition on price), price competition between the original and generic drug rivals, and to parallel traders' activities locally and across each country. In that respect, Figure 9.3.2.2 shows that the highest level of price reduction and price affordability is achieved in countries with higher level of local drug price competition (Bulgaria) and prescribing regulation on drug molecule (Poland). In these countries, price competition fostered by the local prescribing regulation is a sufficient factor for decreasing prices, even without ERP. Another insight could be that the ERP effect is a 'pseudo' price reduction effect, since it just takes the price competition effect from one local market and transfer it to other reference countries markets. This will be further tested through a 'ERP' v a 'no ERP' scenario experiments for a one chosen ERP country market, including scenario variations with contextual market competition factors.

9.3.3 Scenario III: Experimentation for Bulgaria without ERP regulation

The hybrid simulation model presented here is also capable to provide opportunity for scenario experimentation related to a chosen country, and for exploration of the ERP effects in a parallel trade and prescribing regulation context, including what if interventions for policy optimization. Here an example is provided for Bulgaria. ERP regulation in this country is applied at the minimum price level, price revisions are made every half a year and the reference country basket contains the following countries: Denmark, Estonia, Finland, France, Germany, Latvia, Lithuania, Slovakia, Slovenia, Sweden, Switzerland. Local prescribing is mainly made by brand and parallel traders exist. An initial ERP reference mode, tailored to the real ERP regulation parameters for all countries including Bulgaria is performed and exhibited in figures, included in section 9.3.1.

Here, a public policy scenario simulator designed to support what if policy scenario interventions is further configured and its different output explained. Scenario experiments were performed from the perspective of a local price regulation authority, but these also could be done from the perspective of drug company actors, in relation to their public regulation and pricing strategy.

Scenario exploration can be performed also on an EU wide policy level for the support of the efforts of country coordination on finding common and more effective practices of ERP application in relation to ensuring equitable access, availability and affordability objectives in the context of EC goals for the improvement of the functioning of the pharmaceutical systems within EU and minimization and elimination of market failures due to inappropriate national medicines regulation

Figure 9.3.3 (in Appendix F) is a snapshot of a public policy scenario user dashboard tailored for experiments setting and output observation for Bulgaria and selected countries for comparison (AU, BG, HU, PL, LV, SK). This set up can be changed to the specific requirement of the public policy decision maker or from a global and local pricing tactic perspective.

The following settings have been made through the dashboard panel containing the input parameters and their chosen values (numerical or text):

I. Settings for local ERP and contextual regulation (country applying the ERP, reference price calculation formula, reference countries basket and price revision time period, public price discount and year to apply this discount,

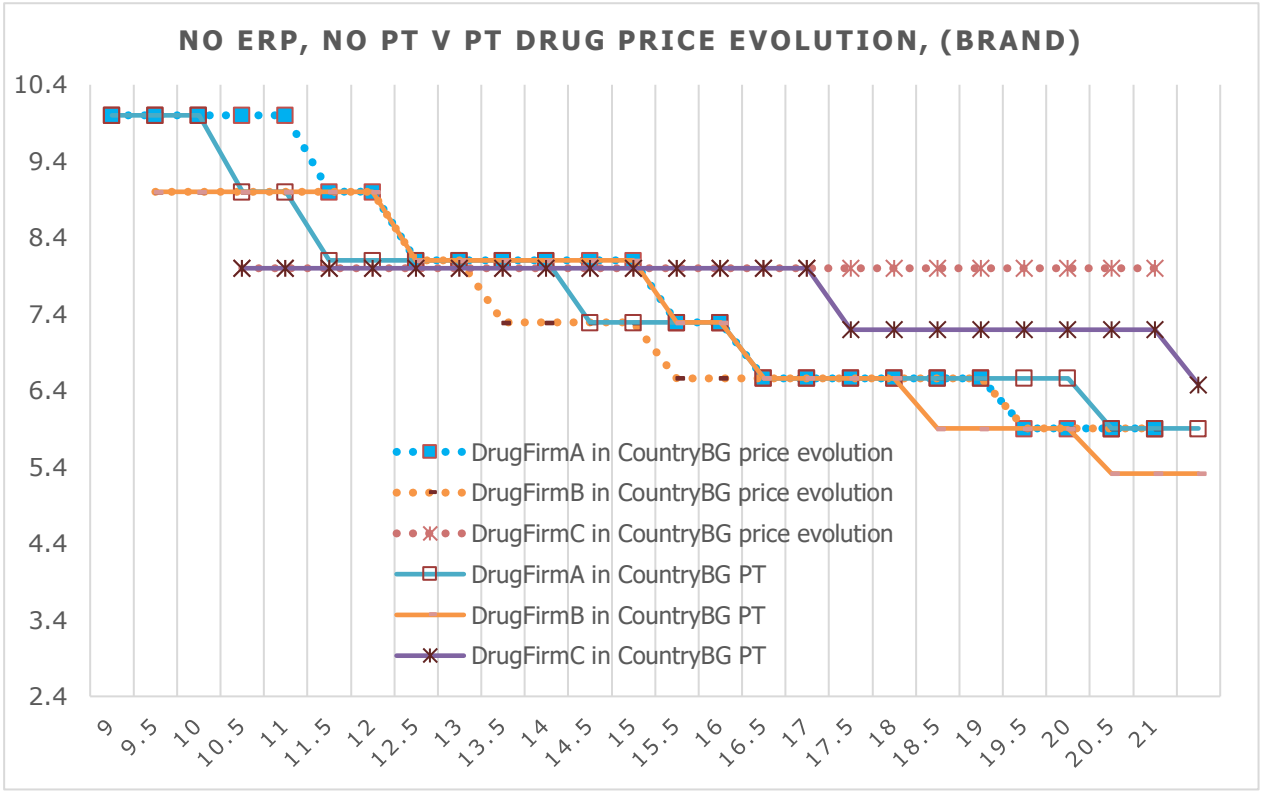
number of countries presence prior to local drug approval, local prescribing regulation)

II. Settings for pharmaceutical firms pricing and marketing strategies (drug min and max price, time of local launch, market share change condition for price decrease, marketing allocation, marketing influence)

III. Parallel traders' activities (active or inactive)

9.3.3 Scenario III.a. 'no ERP, no parallel trade' (innovative or generic brand prescribing) v Scenario III.b. 'no ERP, with parallel trade' (prescribing on innovative or generic brand)

Figure 9.3.3.1 Comparing 'no ERP, no parallel trade' Scenario III.a. v 'no ERP, with parallel trade' Scenario III.b.



In this Scenario III.a. (innovative or generic brand prescribing, branded market), ERP is not applied and there is no parallel trade. There are no drug exits but prices are maintained much higher for longer period of time mainly for one parallel traded drug in comparison with scenario 3b. (innovative or generic brand prescribing, no ERP with

parallel trade). Generic drugs also maintain higher prices but with less difference. Competition works mainly through marketing budget when local prescribing regulation is by brand, which keeps price level higher for longer time especially for the innovative or generic drug, which have better competitive tactic.

When parallel traders are active (Figure 9.3.3.1.), price decrease occurs for higher priced drugs (here drug C). However, an interesting and counterintuitive observation is that the drug that third enters the market with the lowest initial price (Drug C), in both scenario preserves its initial price for longer, this appearing at the end of the shown period, to maintain higher price than its rivals. This appears to come from the effect which parallel traders have on market competition and market shares of the parallel traded drugs. Pharmaceutical companies decrease their drug prices if they lose market share compared to rivals, but at the same time they try to influence prescribing and buying behaviour by allocating marketing budgets, linked to their sales revenues. Apparently, the firm manufacturing drug C, both is object of parallel trade and captures the larger market share on the Bulgarian branded market, which makes the firm refrain from decreasing its drug C price. However, at the same time the effect on price reduction goes to the other rival drugs and mainly to drug A.

Anylogic software dashboard panel for 'no ERP, no parallel trade' and 'no ERP, with parallel trade', price evolution for drug A, B, C in Austria, Bulgaria, Poland, Hungary, Latvia and Slovakia, are provided in Appendix FX (Figure 9.3.3.2.a. and Figure 9.3.3.2.b).

Comparing the drug price evolution patterns between the two scenarios exhibited on Figures 9.3.3.2.a and 9.3.3.2.b (larger graph displayed in the middle), it is evident that the span (difference) between the lowest and highest drug price is higher in the "no parallel trade" scenario versus narrower in the "with parallel trade" scenario. This provides some evidence that parallel traders can support price convergence rather than the opposite.

Figure 9.3.3.2 Comparing 'ERP normal, parallel trade, brand market' reference mode scenario (Scenario I.b) and 'no ERP, parallel trade' (Scenario III.b), brand market and molecule prescribing market

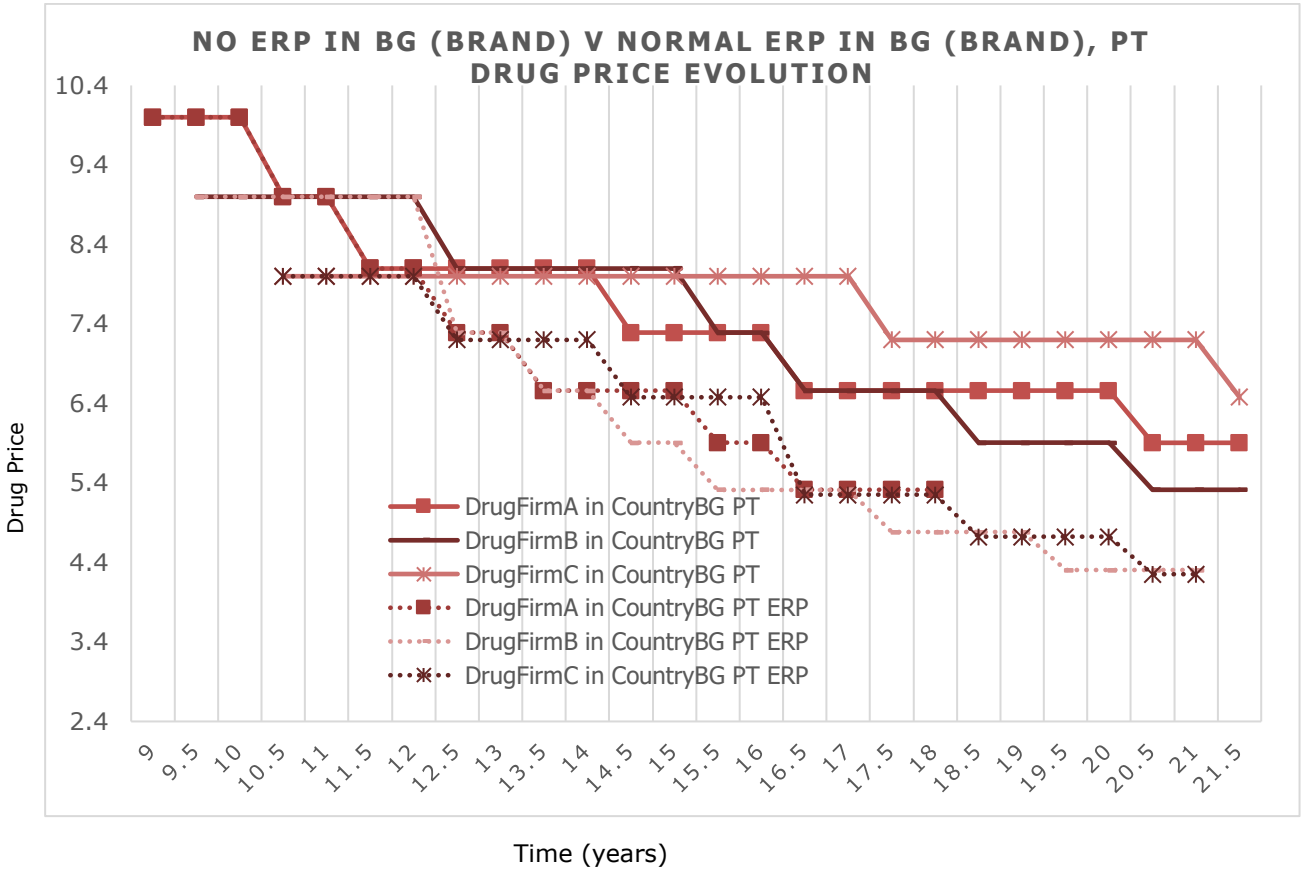


Figure 9.3.3.2 compares 'ERP like normal, parallel trade' reference mode scenario (Scenario I.b) and 'no ERP, parallel trade' Scenario III.b, brand prescribing market. Looking at that comparison on one graph, it is clear that a market with ERP regulation could provide means for more favorable price affordability levels on one side, but on the other it could have effect on drug market exits (drug A exits at year eight after its patent expiration and its monopolistic position on the market, after which it experienced market and price competition from generic drug rivals coming to the market).

Compared to the scenario of 'No ERP, parallel trade, molecule prescribing market' on Figure 9.3.2 b., drug price evolution difference between 'ERP like normal, parallel trade, brand prescribing market' become much less observable in contrast with those between

the two scenarios on Figure 9.3.2 a. It is due to the increase competition on drug price rather than on brand marketing among rival drug companies.

9.3.4 Scenario IV: Comparing 'No ERP, parallel trade, molecule market' scenario IV.a and 'ERP, with parallel trade', brand market scenario IV.b.

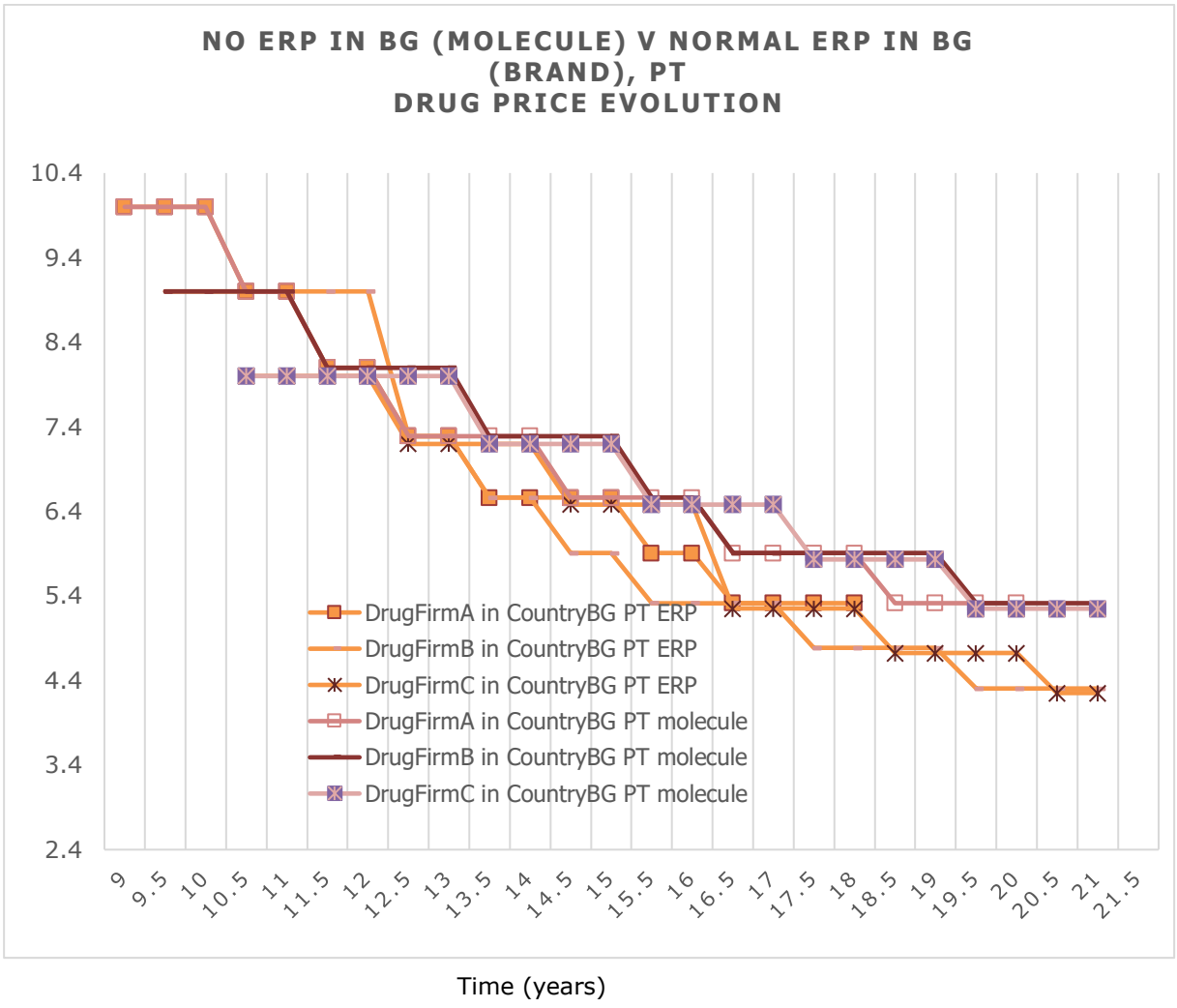


Figure 9.3.4.1. Comparing 'ERP like normal, parallel trade, brand market' reference mode scenario and 'no ERP, parallel trade', brand market and molecule prescribing market

Price competition (if prescribing by molecule) and if ERP is not applied, can have counterintuitive effect (Figure 9.3.4.1 above) on drug availability (innovative off patent drug A exiting at about year 10 after patent expiration), compared to the ERP reference mode scenario (regular price revisions with prescribing by brand). This effect could be attributed to the local prescribing regulation, which if connected to molecule prescriptions, could intensify further local market price competition. This is evidence for

the favourable effect on affordability of a local prescribing regulation which fosters price competition. A combination like that can ensure that if any drug market exits occur, they would not be due to the ERP regulation and price cross country referencing feedback effect.

Furthermore, the ERP can be applied not as a price setting tool but instead as a price negotiation tool to support local pricing authorities against the market power of drug companies. Also ensuring prescribing by molecule would ensure higher price competition local effect. In countries with limited market and price competition (with fewer rival drugs and or local prescribing is done on innovative or generic brand), ERP configured to regular benchmarking with drug prices from local markets with higher competition level, could be a good tool to offset oligopolistic pricing behaviour on that local market.

9.3.5 Scenario V: With ERP countries variation in Bulgaria, excluding countries Greece, Sweden and Netherlands (brand prescribing)

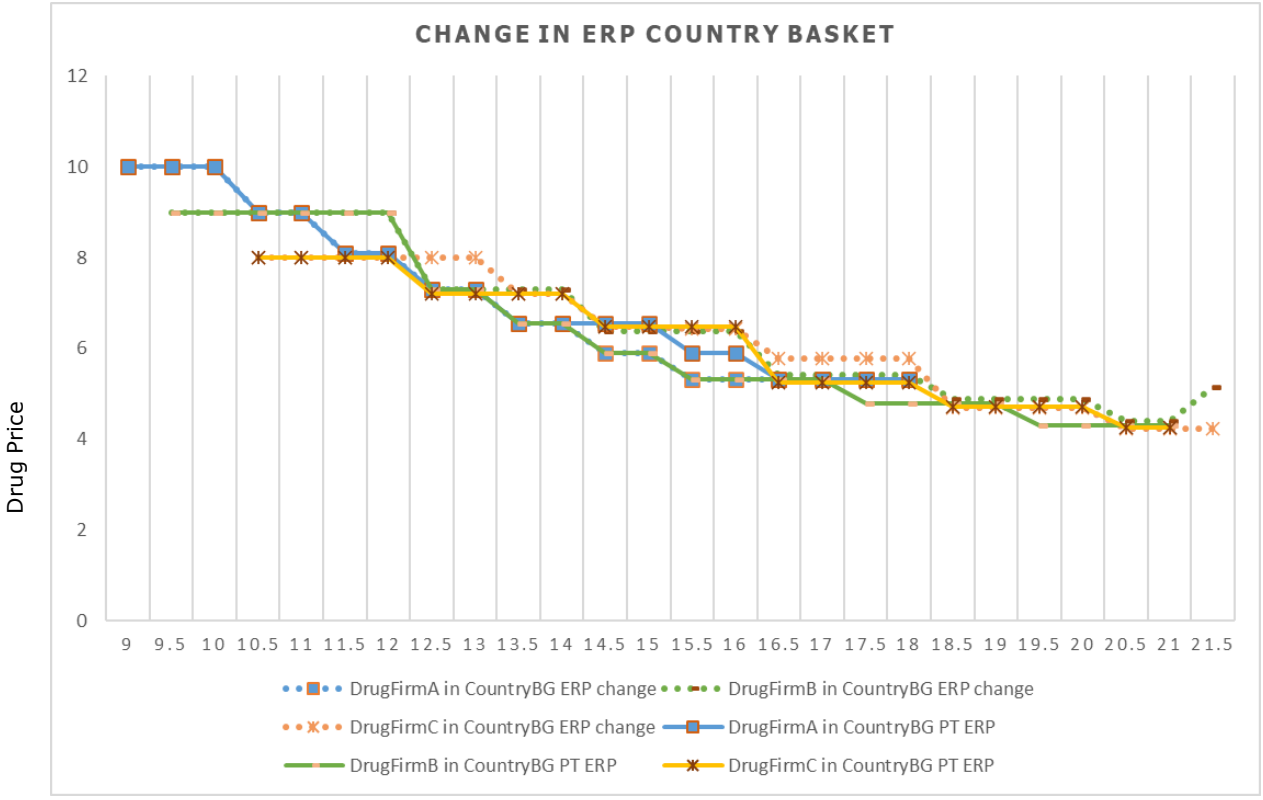


Figure 9.3.5.1 ERP reference basket variation scenario V.a. v scenario V.b. (excluding Greece, Sweden and Netherlands v normal ERP (including these countries)

The reference country basket variation scenario is made for demonstration example only, by excluding three countries like Greece, Sweden and Netherland. The reasons are that these countries have different economic and social parameters compared to Bulgaria. The outcome is similar to the initial scenario (containing the above countries in the reference basket) with the difference that drug B and drug C get a little higher prices and drug A lower, but the price evolution pattern remains the same. This experiment shows that variation in reference country basket can produce effects which do not coincide with expected outcome, which is due to the high level of drug price referencing among all ERP countries.

A large number of scenarios with variations of the above parameter (combination and number of countries selected for reference country basket) could be purposefully set according to each country price authority criteria requirements, however a parameter variation experiment including all possible combinations would be hardly performable. This is due to the fact that if for example, such experiment is configured for total number of countries N = 30, and for a country basket of number of countries K = 10, then the total number of all NK variation experiments would be equal to approximately 30 million runs. That is why, the selection of combination of parameters for parameter experimentation was considered in line with the scenarios generated through the RAM analysis in the previous qualitative modelling stage. Another important issue for combined exploration is the global effect of local state public price discounts which will be further evaluated in the next scenario experiments

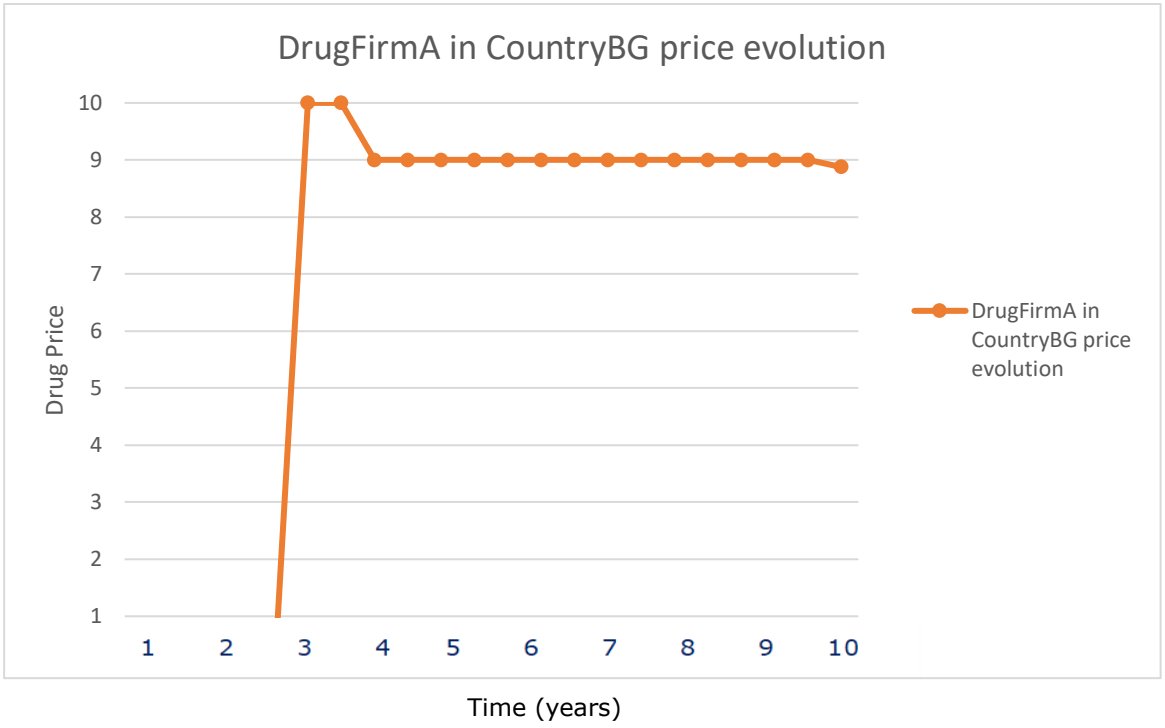
9.3.6 Scenario VI: simulation with state public discount at drug launch on the local market

The first scenario explored (after the above settings have been introduced through the user dashboard) is connected to exploring the ERP effect of a state public price discount on the local drug price evolution, including a requirement for drug A presence in four countries prior to drug market local price approval.

Figure 9.3.6.1 presents a graph on the first ten years of innovative drug A price simulated evolution, after it entered the local market and in parallel other EU markets included in the simulation model. In this period, drug A is still having patent protection and there is no competition with other drugs on the EU market. The outcome shows that, drug A entered local Bulgarian market with delay of five years (due to the requirement for drug A presence in at least four countries prior local approval). It experienced a discount of 10% in its price once at market entry, due to the local price regulator

requirement. It is evident that price decreases have one off effect after which price remains at the same level throughout patent protection period, after which it starts to decrease (after the entering of rival generic drug products, presented on Figure 9.3.6.1).

Figure 9.3.6.1 Price evolution of drug A



It is interesting to observe what parallel trade can contribute to the drug A affordability level and how their activities effect ERP. Parallel traders appear to buy drug A from their local markets, where drug A price is lower and sell it to Hungarian market where drug A price is higher, in order to take benefit of drug A price difference (parallel traded drug prices are shown on the graph of Figure 9.3.6.2, and country markets where these drugs are sold are shown in the list on the same figure, including which trader sells which drug). This brings benefit to the price affordability level in Hungary offering the same drug to local patients on lower prices. Due to the fact that parallel traders compete for about ten percent of the market share of the traded drug which maintain monopolistic position on the market without other generic drug rivals, their activities cannot incentivize the initial drug A public price to decrease, which do not interfere with the ERP regulation effect on the market.

The global effects of ERP regulation related to a state public price discount introduction in one local country market can be observed on the following Figure 9.3.6.3, where drug A price evolution in a group of selected countries is presented for comparative observation.

Drug A public price discount decrease in Bulgaria is transferred through the ERP local rules in full only in one local market of Slovakia and indirectly once in AU and in PL and LV in a gradual averaged decrease through the ten year period due to the local ERP price calculation and reference country basket differences. Hungarian local market price remains at its highest initial level and unaffected and this is the reason to attract parallel traders which compensate for the lack of competition, for the high price of drug A and for the inefficient ERP local tool box to bring lower prices from other reference basket countries, where state public price discounts were imposed or efficient competitive environment and factors like rival drugs and parallel trade have further developed.

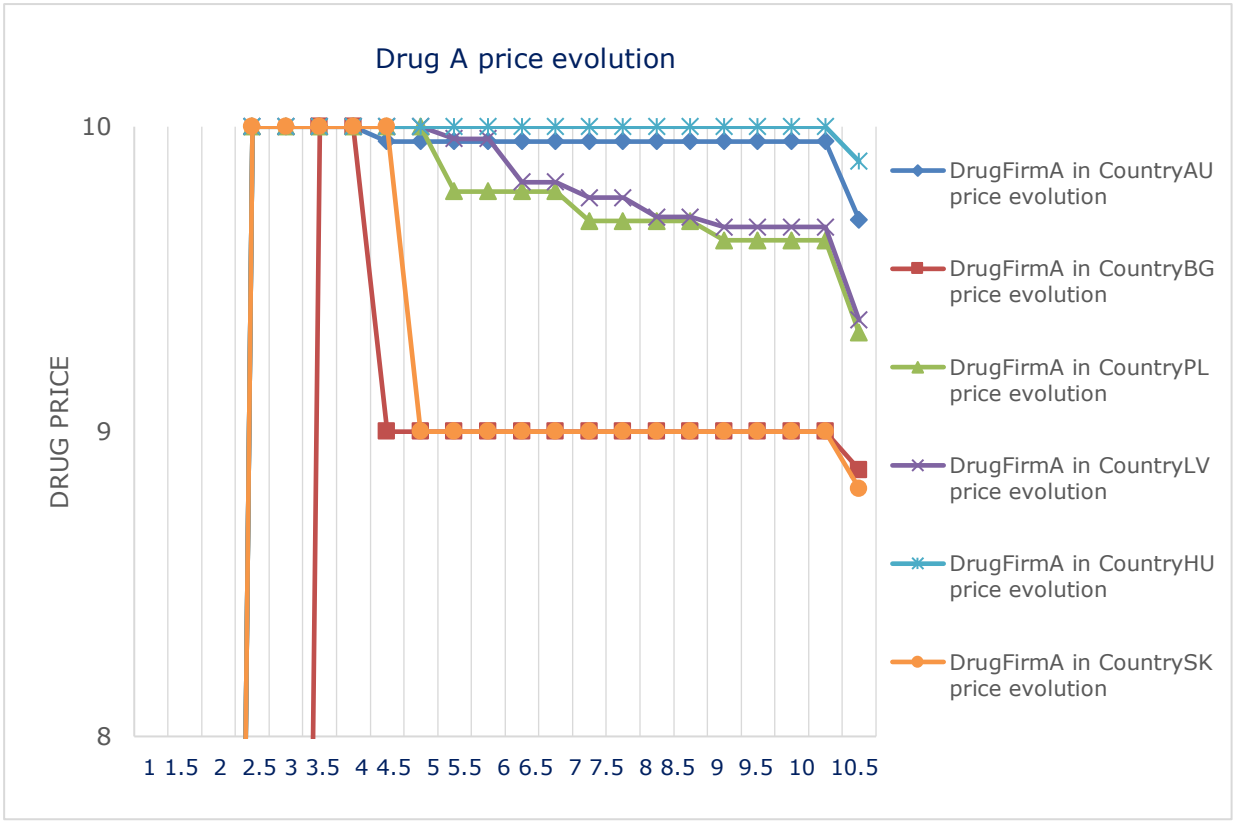


Figure 9.3.6.3 Drug A price graph for comparing price evolution among six selected countries (Austria, Bulgaria, Poland, Hungary, Latvia and Slovakia)

The above simulation experiment shows that changes in the ERP regulation in one country can have both direct and indirect effects throughout all other ERP countries, depending on local ERP rules, which are interfering with local prescribing regulation, parallel trade and competition level (one or more drugs competing on a local market).

9.3.7 Scenario VII: with generic drugs competition after patent expiration of the innovative drug

Exploring further the evolution of drug prices after drug A patent expiration and the entering of two generic drug rivals in year 9 and year 10 (Figure 9.3.7.1), shows that prices start to decrease for all available drugs, due to market share competition, leading to no drug withdrawals of the Bulgarian local market. In regard to the affordability criterion, public drug budget spending becomes lower. In this like in the previous scenario, the ERP regulation is set to capture competitive price discounts in full and to use them to change public prices, due to which it can further transfer changed public prices among reference basket countries with different price competition level.

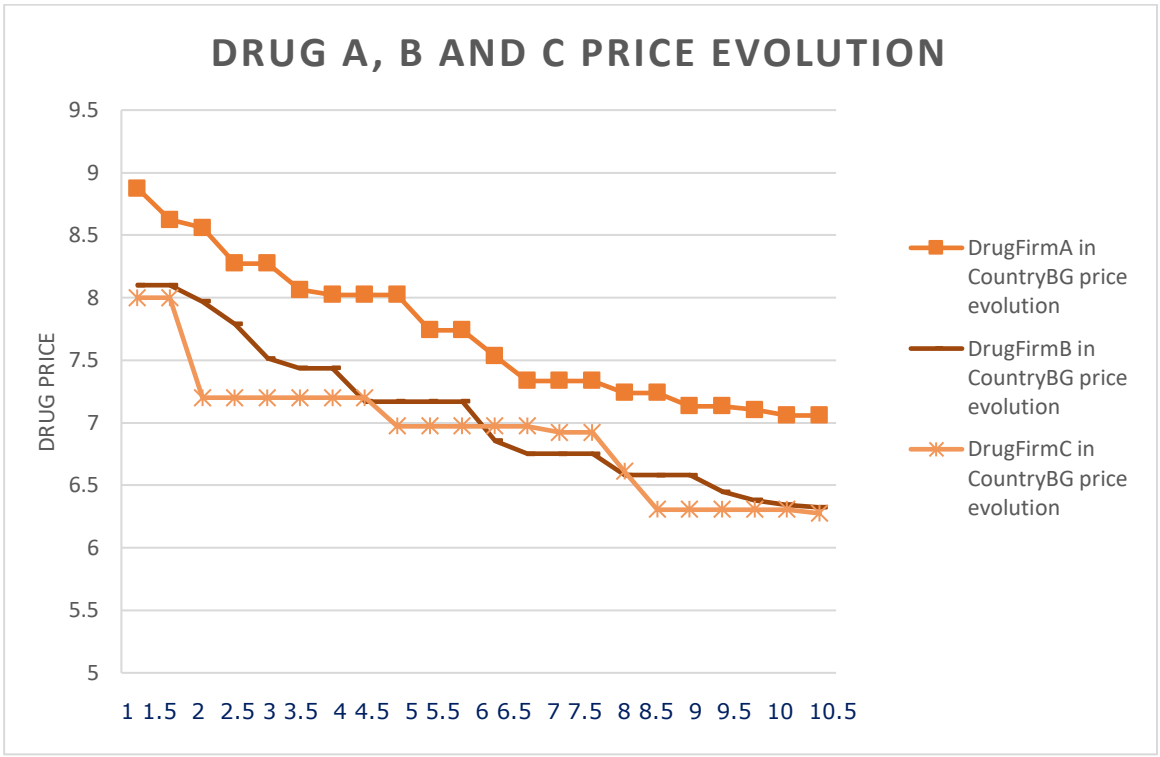


Figure 9.3.7.1 Evolution of drug prices after patent expiration of drug A

All local parallel traders buy locally and sell among attractive EU markets looking for higher price differences in order to make profit (Figure 9.3.7.2 in Appendix F). For example, Trader1 buys drug B from AU and sells to BE, while Trader2 buys drug C from BE and sells in AU, and Trader 3 buys drug C from BG and sells to AU. All other local traders and their drug buying and selling activities are also listed on the right side of the graph.

The next graph (Figure 9.3.7.3) shows comparative drug price evolution among selected ERP countries and their respective interlinkages through their local ERP rules set. For example, drug A price evolution in Austria compared to drug A price in Bulgaria, provides observation that no drug convergence appear between the two prices of the same original drug. Further, comparing drug B prices in the same countries, confirms the above observation of no price convergence behaviour. This can be explained with the differences between the ERP rules for both countries and also, with differences between local competition contextual conditions like intensity of competition, parallel trade activities and prescribing regulation.

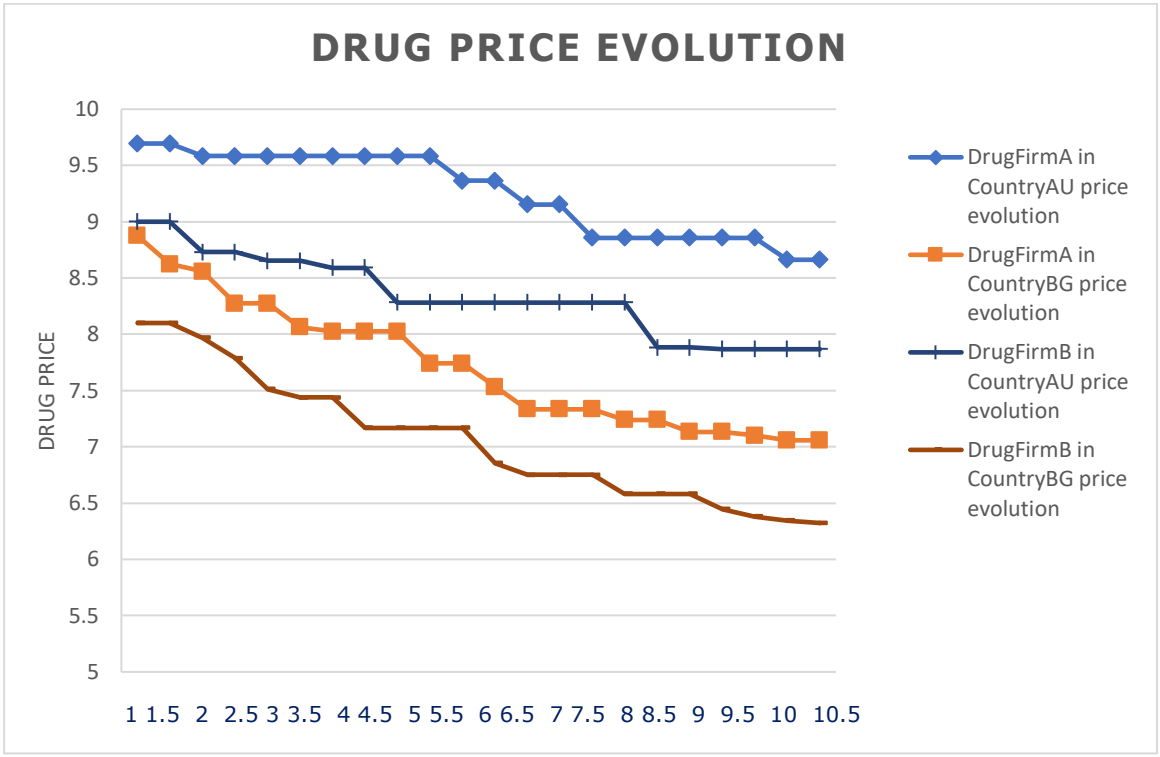


Figure 9.3.7.3 Comparative graph for drug price evolutions after patent expiration of the original drug (among selected countries)

Further, comparing drug A prices in BG and in AU can explain the parallel trader behaviour to buy from BG and sell to AU due to making highest benefit of drug A price difference among the two countries. Another observation is that, because prices do not converge over time, this gives room for parallel trade activities and parallel trade effects.

9.3.8 Scenario VIII: Comparative experiments with real data, ERP vs. No ERP

On the next figures, comparative scenario experiments are provided for Bulgaria. These scenarios are related to evaluating the effectiveness of the present ERP regulation, which is used as the reference base case for comparison.

The reference base case consists of the following: drug price calculation is on the 'min' reference price, price revision period is on one year and reference pricing basket consists of countries according to the local legislation data), parallel trade is active and prescribing regulation is on 'brand'. The reference case is then compared to 'No ERP' scenarios within the same local market and regulation context.

These scenario experiments are performed with the assumption that the ERP regulation can capture drug market price discounts, which pharmaceutical firms are using to compete with their local rivals. This is done, in order to provide ERP comparative evaluation within conditions when the ERP could provide the most effective results. It should be noted that in most of the times, competitive price discounts remain hidden and thus, the ERP regulation cannot use them in the calculation of public drug prices among EU markets.

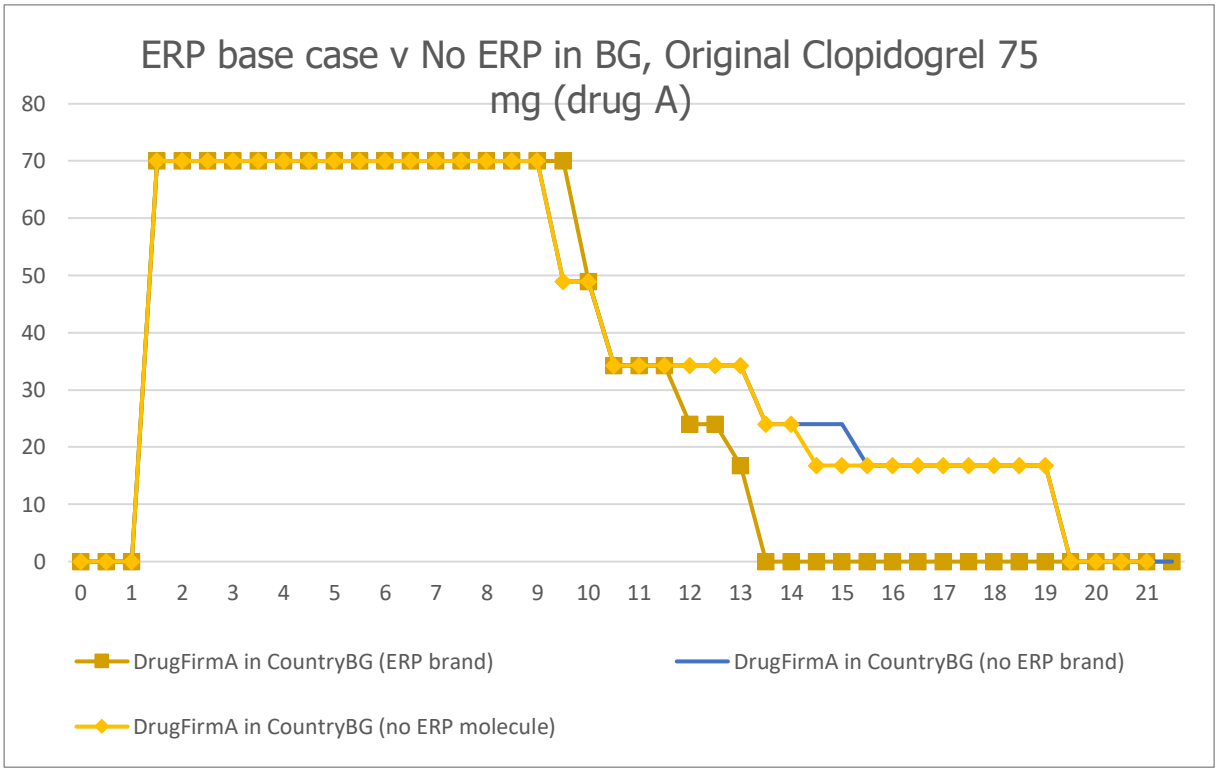


Figure 9.3.8.1 above presents ERP in Bulgaria base scenario compared to two other 'No ERP' scenarios (prescribing on 'molecule' and prescribing on 'brand') for original clopidogrel 75 mg.

First observation is that there is no difference in the original drug price evolution in the first ten years (patent protection period), no matter which scenario is performed. This provides a clear indication that the ERP regulation is not effective when drugs have patent protection and there are no other rival drugs on the EU markets. After the market protection expires and generic drugs enter the market, bringing price competition, then all drug prices begin to decrease. The original drug A price decreases most quickly in the ERP base scenario, in comparison to all others. However, in the ERP base scenario, the drug A exits the market three years after patent expiration, while in the other scenarios drug A stays further 4 and 6 years on the market. On one side, the above comparison gives evidence that the ERP regulation can be effective when applied in a competitive market, in contrast if applied in a monopolistic (on patent) market. On the other side, this scenario experiment further showed that the ERP regulation can lead to drug market exits. These results provide further insight into the trade off problem between the two criterion of drug price affordability and drug availability on a local market.

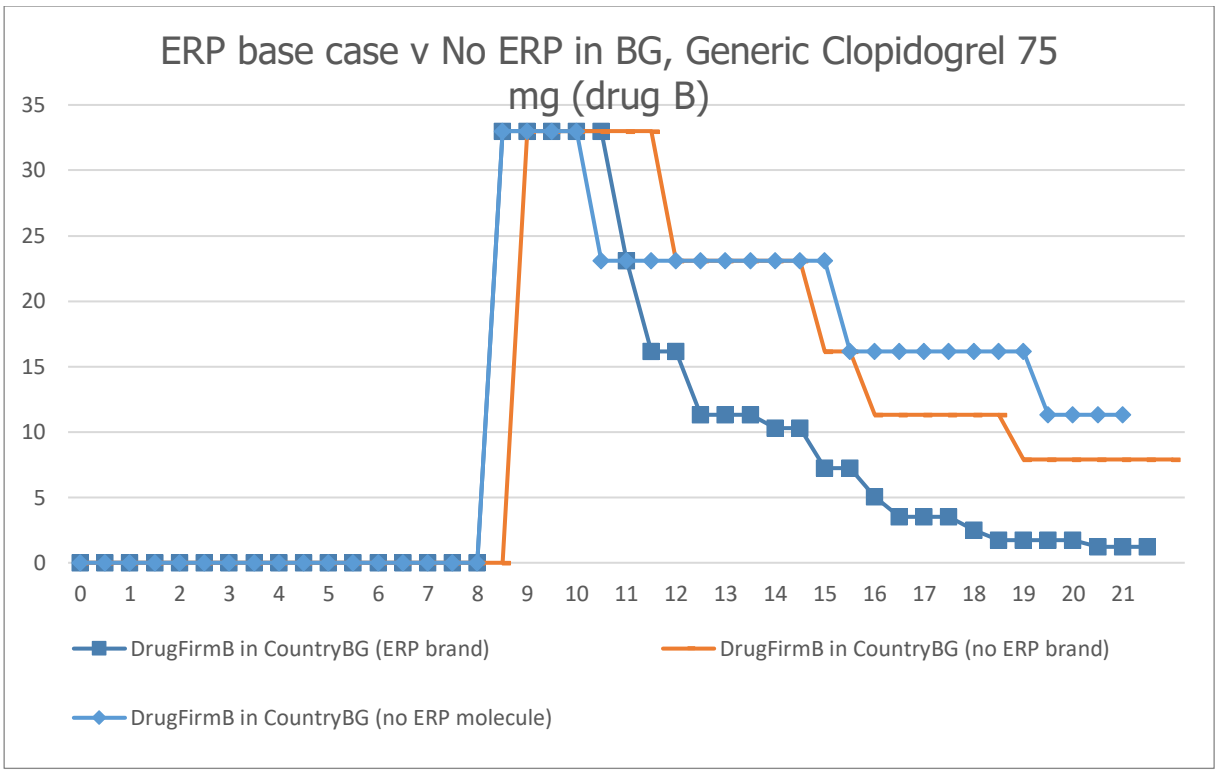


Figure 9.3.8.2 above presents ERP in Bulgaria base scenario compared to two other 'No ERP' scenarios (prescribing on 'molecule' and prescribing on 'brand') for the first to market generic clopidogrel 75 mg.

The Figure 9.3.8.2 above presents the same scenarios results for the first generic clopidogrel (drug B), which enters the local market after patent expiration of the original clopidogrel (drug A). This experiment provides evidence in favour of the ERP regulation base scenario, which decreases the price of drug B to the highest extent (providing that drug B does not have a lower price threshold, after which it must exit the local market).

Another result is that, scenario 'no ERP' combined with drug prescribing on 'molecule' can lead to higher drug price levels, in comparison with 'no ERP' combined with prescribing on 'brand', in contradiction to the belief that prescribing on molecule fosters price competition, which decreases prices more than prescribing on innovative or generic brand. This showed that there are other factors, like parallel trade, which can foster drug price competition (even higher when prescribing is on innovative or generic brand), and thus can provide conditions for further price decrease and drug affordability in certain countries. Another consideration could be made in regard to the pharmaceutical firm tactics to withdraw their drugs after a certain price threshold, which further could hinder the ERP regulation effectiveness in connection to the drug availability criterion.

The same consideration are valid when observing the scenario results for the second generic clopidogrel, coming to the local market (Figure 9.3.8.2). Again, the ERP regulation base scenario looks like providing the best results in relation to the affordability criterion, but leaves doubts if pharmaceutical firms tactics include drug exits after a certain price threshold is reached in an ERP regulation market. Here, the closest 'no ERP' scenario to the ERP base scenario is when the local prescribing regulation is on 'molecule', thus proving evidence in support to the belief that prescribing on molecule fosters drug price competition, which further decreases drug prices on a local market.

Brand prescribing, on the contrary, provides results in support to the opposite, price competition is not or is much less supported when drugs are prescribed like brands and pharmaceutical firms use marketing budgets, rather than price discounts, to compete on the market with their rival companies.

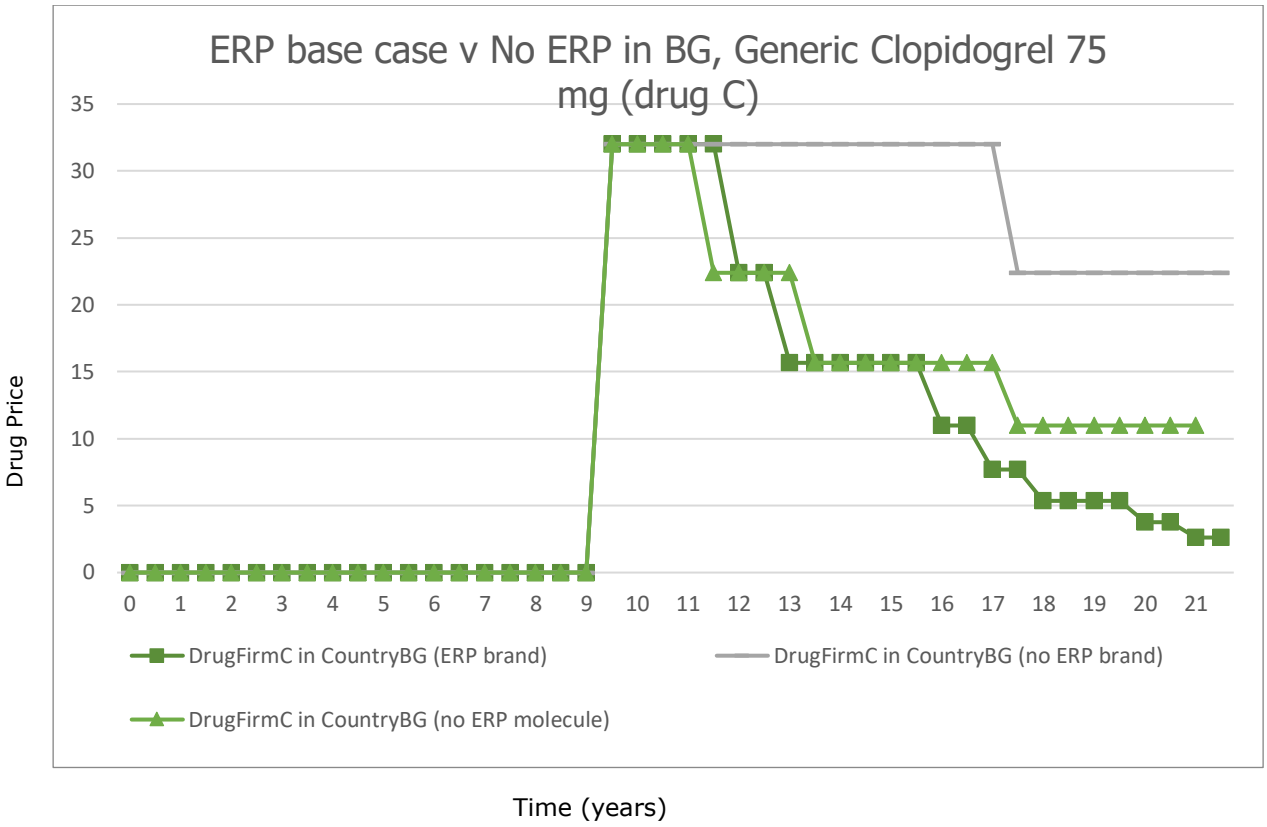


Figure 9.3.8.3 above presents ERP in Bulgaria base scenario compared to two other 'No ERP' scenarios (prescribing on 'molecule' and prescribing on 'brand') for the second generic clopidogrel 75 mg.

9.3.9. Scenario related simulation experiments IX: Parameter variation experiments

Next, the following parameter variation (PV) experiments have been done, changing main ERP tool set and local prescribing parameters (price calculation on 'min' or 'avg', time period for revision of prices on one or two years, and local prescribing on 'brand' or 'molecule').

Comparing PV scenario experiments on variations in main ERP tool set and local prescribing parameters (price calculation on min or avg, time period for revision of prices on one or two years and local prescribing on brand or molecule), can support confidence building, showing output results consistent with documented statements and market logic (market functioning and changes expectations).

This PV experiment is run two times with two different assumptions, first if ERP regulation could capture market competition price discounts in full and second if the ERP could not capture market competition price discounts at all or to a limited level.

Figures 9.3.9.I and Figures 9.3.9.II and Figure 9.3.9.III (in Appendix FX) for drugs A, B and C exhibit eight possible combinations each, between the values of the three parameters of the ERP regulation price calculation, ERP drug price revision period and prescribing regulation: ERP on 'min', ERP on 'avg', revision period of one or two years and prescribing on 'brand' or ''molecule'. This can support the exploration of the combinatorial effects of the different ERP and contextual prescribing regulation changes on the drug price evolution and can produce important insights regarding ERP regulation evaluation against main criteria of equitable access, affordability and availability of medicinal products in EU and around EU local markets.

It can be clearly observed on all of the graphs regarding drugs A, B and C, that highest prices occurred when the ERP regulation uses drug price calculation on avg and price revision period on two years, combined with local drug prescribing regulation on brand. On the contrary, the lowest drug prices can be achieved if the ERP regulation uses drug price calculation on min and price revision period on one year, combined with local drug prescribing regulation on molecule.

Main insight from the above is that contextual prescribing regulation on molecule plays an important role in fostering local market price competition, which can be transferred to other reference basket countries, but when local prescribing is on brand then prices are kept higher, which again are transferred through the ERP local rules to other local markets.

Also, it is clear that neither of the variations in the selected parameters influence prices of on patent innovative drugs. This is a clear insight that ERP regulation does not and cannot work if there is no drug price competition on the market or a state public price discount requirement, meaning it cannot reduce public prices of innovative patented drugs if there are no other price decreasing conditions.

When ERP cannot capture market price discounts (where pharmaceutical companies compete on hidden price discounts along the value chain), then public prices are higher and are transferred throughout the reference basket local markets using the ERP regulation, while the market prices can change more often due to hidden competitive discounts which remain uncaptured.

However, if ERP regulation could take account of market price competition and price discounts in full, then drug price affordability level would be much higher but can lead to

drug market exists, except in most favourable combination of ERP tool set components (price calculation on avg and not on min, longer price revision time period) and local prescribing regulation on brand v molecule (Figures 9.3.9.I, II, III). Because of the above described effects, a trade off occurs between the aim of ERP regulation to provide higher affordability and the drug availability lower level countereffect. In this respect, ERP can be more suitable for application in countries with local prescribing regulation on brand, providing market competition price discounts are official and could be captured within the ERP tool set. If ERP is applied where there is an active IRP regulation for reimbursement purposes, then the on patent drug prices could be further decreased due to the generic drugs price competition within the therapeutic or disease groups.

However, the above experiments use the assumptions that the ERP is capturing the market competitive price discounts, depending on pharmaceutical companies competition tactics. Here, these are connected to 10% price discounting if the relevant drug decreases its local market share with 10%, in comparison with the previous time period.

In this respect, another parameter variation experiment is set to account for the uncertainty in the extent to which market competition discounts could be captured in the ERP framework. The eight combinations of the selected ERP and prescribing regulation parameter values from the previous experiment have been simulated in one hundred runs, using different market price discounts within the range of 0.01 to 0.10 of the public prices. All simulation output graphs have been included in Appendix FX to this chapter. Price evolution data sets have been copied from the Anylogic output and statistical analysis has been performed with MS Excel (Appendix FX to this chapter), presented in the next section 9.3.10.

9.3.10 Uncertainty analysis of the ERP regulation

This section includes uncertainty analysis of the ERP level of capturing market competition drug price discounts (pharmaceutical firms market price tactics), combined with parameter variation: min or avg price calculation, innovative or generic brand or molecule local prescribing, parallel trade and initial state discount for innovative drug, compared to a 'no ERP' regulation market.

All ERP policy experiments regarding drug price evolution, including comparing different policy scenarios (with or without ERP, prescribing on brand or on drug molecule) are each run 100 times (comparing drug prices means), with price discounts generated as stochastic data (within min. to max. percentage interval), in order to compensate for the

uncertainty of the extent to which ERP regulation can capture real market drug prices for public price referencing purposes.

9.3.10.1 Description of the ERP regulation what if scenarios

Visual comparisons between the statistical means of the compared scenario simulations have been done on the distributions of drug A price, drug B price and drug C price for the following scenarios.

1. The first scenario is about external reference pricing regulation with price calculation on minimum price (among reference basket countries) and prescribing regulation on molecule.
2. The second scenario is the same as the previous one but without external reference pricing regulation application.
3. The third scenario is like the first one, but prescribing regulation is on brand.
4. And the fourth scenario is like the previous one but without external reference pricing application.

The simulation was performed in 100 runs for each of the above scenarios, with the goal to capture enough wide sample of drug price distributions, with variability in the degree of the ERP regulation to capture the full market price discount (within 0.01% to 0.10% of the public price), within a 95% of confidence interval. Drug price statistical means of each run have been analysed in MS Excel, in order to compare the above mentioned scenarios.

The results showed that all drug price mean distributions are a statistically significant outcome of different independent variables with 95% of confidence. Also, the analysis proves that the results of the compared scenarios (the means of each 100 runs) are not due to random factors.

All this means that public price levels depend with 95% confidence, both on the ERP and contextual regulation, no matter what would be the degree of capturing market price discounts through the external reference pricing regulation. Also this means, that both the ERP and contextual regulation can produce effects on drug of market drugs availability on a local market.

This produces an important question about the contradiction between drug price affordability and drug price availability and how public price authorities should find a way to cope with this issue.

Figures 9.3.10.I.A, 9.3.10.I.B, 9.3.10.I.C and Figures 9.3.10.II.A, 9.3.10.II.B, 9.3.10.II.C provides comparative results of the drug price distribution means and tables 9.3.10.1.a and b, 9.3.10.2.a and b, and 9.3.10.3.a and b (in Appendix FX) provide analysis of variance indicators showing that there are statistically significant differences among all scenarios that have been used for comparative purposes. In all four scenarios for each drugA, drug B and drug C, the values of F critical are lower than the values of F (intergroup mean variance is higher than the intragroup variance)m which provides statistical proof for rejecting the null hypothesis that there is no statistical difference among the compared scenarios.

What is interesting is the counterintuitive comparative results that price affordability level in scenario when there is no external reference price regulation with prescribing on molecule is and almost coincides with the scenario when there is external reference price regulation, but prescribing regulation is on "brand" for drugs A, drugs B and is even better for drug C.

This observation questions the usefulness of external reference price regulation in connection to the contradiction between drug price affordability and drug availability. This proves the hypothesis that drug price competition plays the main role in rising drug price affordability levels while external reference pricing regulation can just transfer direct or indirect price levels from one competitive market to other less competitive markets and or vice versa.

The price inflation hypothesis is also proved in the patent protected markets and in markets where external reference price regulation coexists and interferes with brand prescribing regulation, this way transferring higher level prices compared to the scenario with "molecule" prescribing regulation which fosters higher market price competition.

Here, a comparative analysis is made on Figures 9.3.10.I.A, 9.3.10.I.B, 9.3.10.I.C and Figures 9.3.10.II.A, 9.3.10.II.B, 9.3.10.II.C. These graphs represent statistical means of the simulated price evolution for drug A and drug B and drug C in two main scenarios sets:

I. Market "with ERP" and reference price calculation on "min" compared with a "no ERP" market. Both scenarios include public price state discounting, parallel trade, and either innovative or generic brand or molecule prescribing.

II. Market "with ERP" and reference price calculation on "avg" compared with a "no ERP" market, including public price state discounting, parallel trade and either brand or molecule local prescribing

The purpose of this "with ERP" v "no ERP" comparative scenario analysis is to assess the level of effectiveness of the ERP regulation against a hypothetical 'no ERP' scenario, in connection to the main criteria of access, affordability and availability of innovative and generic drugs on the local markets in EU.

This simulation comparative effectiveness analysis is the first simulation assessment of the ERP regulation effectiveness. This approach follows main principles for public policy evaluation through using computation simulation for comparing different policy v no policy scenarios and their effectiveness against selected outcome criteria (Gilbert et al., 2018) . Also, it is the first in respect of taking account of the parallel traders' activities, drug suppliers pricing and market strategies, connected to their market sales volumes and share, drug budget expenditure, public price discounts and local prescribing regulation. This ensures a comprehensive systems analysis of the ERP and outperforms the previous simulation analysis performed for the European Commission, which has been connected to a price evolution DE analysis without taking into account all the above systems components and missing the perspectives of access and availability of medicinal products, while taking a narrow perspective of affordability connected to state public price discounts transferred among the reference basket countries through the ERP local countries rules.

9.3.10.2 Market with ERP and reference price calculation on min compared with a no ERP market, considering effects of parallel trade, and either brand or molecule prescribing.

9.3.10.2.A Scenario with ERP: Market with parallel trade, state drug price discount for market entry, prescribing on brand or on molecule, ERP calculation on minimal reference price, price revisions once per year (PT MEPD brand or molecule, price calculation on min, price revision period one year).

All comparative graphs (9.3.10.I.A, 9.3.10.I.B, 9.3.10.I.C and 9.3.10.II.A, 9.3.10.II.B, 9.3.10.II.C) show four drug A, drug B and drug C price scenario evolutions for a simulated 45 year time period, where:

1. the simple grey line represents the mean of drug A, drug B and drug C price when the ERP calculation is set on min, prescribing regulation is on molecule

2. the yellow diamond line represents the mean drug A, drug B and drug C price when the ERP calculation is on min, but local prescribing is on brand (which represented the real ERP regulation setting, against which other what if scenarios are compared)

3. the blue dashed line represents the mean drug A, drug B and drug C price when there is no ERP, prescribing is on molecule

4. the dotted line represents the mean drug A, drug B and drug C price when there is no ERP, but prescribing is on brand

In addition, the graphs shows the effect of a public price state discount of 10% introduced at year two of drug market entry and a requirement for drug presence in three ERP countries prior to drug price approval and market registration.

Vertical lines on the graphs mark drug time delay, drug patent protection expiration, and percentage of drug A unavailability on the market (presented as averaged number of years during which the drug is not present on the market for all 100 runs, divided to the simulated time period).

Looking at the graphs, first period of patent protection and no competition of drug A shows no ERP effect on price decrease in all scenarios but on the opposite, ERP supports price maintaining on its highest level. Even after the introduction of a public price state discount, drug A price decreases once and continues to stay stable until patent protection expiration and coming of the generic drugs' competition Drug A enters the market with two years delay due to an external price approval requirement for drug presence in at least three other ERP markets prior to its local launch.

Scenario 1 shows that external pricing reference effect on price affordability is highest after the patent protection period, decreasing drug A price to the lowest level compared to the other scenarios. On other side its effect on maintaining drugs' availability is lowest compared to the other scenarios (84% not available on the local market). The public price is higher when prescribing is on brand (scenario 2, but it almost coincides with drug A price when there is no ERP and prescribing is on molecule (scenario 3). In both scenarios, drug A could be unavailable in 53 % and 64 % of the simulated time period If there were no ERP and the prescribing were on brand, then drug A would have achieved the highest price hence the lowest level of affordability for public budget and out of pocket expenditure (scenario 4).

The best policy option for drug A would be 'no ERP' policy and local prescribing regulation on molecule, which could bring best balance between affordability and availability of

innovative off patent medicinal products If drug A market exits occur in this option, they could appear because of market competition and not because of the ERP effects.

Figure 9.3.10.1.a and Figure 9.3.10.1.b exhibit parameter variation experiments output window of Anylogic software (in Appendix F). Parameter variations are performed including stochastic uncertainty parameter for market price discounting from 0.01 to 0.10 %, which provides a proxy for the drug price competitive discounts degree of uncertainty of being officialized (disclosed in the public drug price) and thus captured by the ERP regulation on a "with ERP" market scenario (Figure 9.3.10.1.a), and on competitive drug price discounts on a "no ERP" market scenario (Figure 9.3.10.1.b), including variation in the prescribing regulation ("brand" or "molecule").

The four output price evolution data sets (related to each of all four scenarios) for drug A have been copied and analysed in MS Excel. Descriptive statistics have been done for calculating drug price means, within 95% confidence interval, standard deviation etc. Appendix F. After that, drug price means for each scenario have been put together for comparison on a separate graph (Figure 9.3.10.I.A). In addition, the statistical analysis performed for all four drug price data series showed that all scenarios and their price distributions are statistically significant and are result not from random variations but from differences in the main parameters ("with ERP" vs "no ERP", "brand" vs "molecule").

9.3.10.2.B Scenario without ERP, PT MEPD brand or molecule

The results of the parameter variation with market price discount uncertainty analysis, exhibited on Figures 9.3.10.1.a and 9.3.10.1.b (in Appendix FX), provide the following insights:

- First, there is a large span between the lower and upper boundaries of the resulting drug price evolution, thus accentuating on the importance of the market drug price discount parameter;
- If the ERP regulation can capture market price discounts, this would lead to high affordability (lower public drug prices) but also to higher level of drug unavailability (drug market withdrawal);
- If the ERP regulation cannot capture market price discounts, resulting from drug price local market competition, this would lead to lower level of affordability (public drug prices would decrease with much lower rate), but on the other side, fewer drug market withdrawals would appear resulting in higher level of drug local market availability.

- The above results present a contradiction leading to an important trade off conflict within the ERP regulation and to a need to find how to strike a balance between this trade off tension between the affordability and the availability criteria;
- These results also confirm that the ERP regulation could just "control" prices, which are officially registered on the public price lists and thus can transfer their evolution between reference basket countries;
- Further, these results, as also evident on the next Figure 9.3.8.I.A (presenting statistical mean drug prices for the four scenarios explained above), provide the insight that the local prescribing regulation, can have interfering effect with the ERP regulation and on drug price evolution, due to affecting price competition tactics of drug companies: 'brand' prescribing sustain higher drug prices and lower rate of price decrease in time, in comparison to 'molecule' prescribing regulation, which fosters price competition and quicker price decrease.

All the above insights are also evident on the next 9.3.10.I.B, and Figures 9.3.10.3.a, 9.3.10.3.b and 9.3.10.I.C, which present parameter variation uncertainty results for drugs B and C.

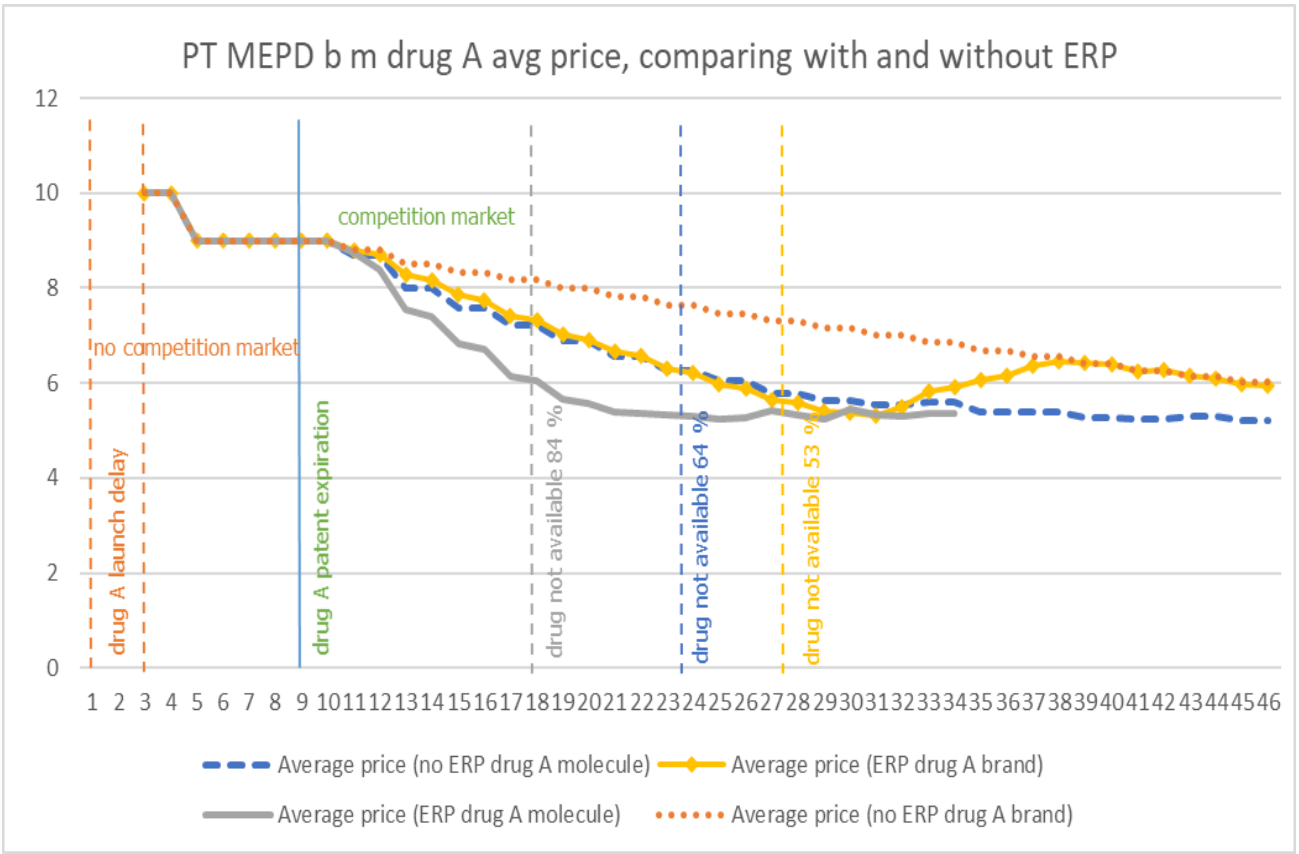


Figure 9.3.10.I.A Comparing statistical means of drug prices from 100 runs for all four scenarios (drug market price discounts are made stochastic): ERP base case from section 9.3.8 for Drug A versus ERP regulation with 'brand' prescribing, 'No ERP' regulation with 'brand prescribing' and 'No ERP' regulation with 'molecule' prescribing.

Figure 9.3.10.I.B exhibits the price evolution of drug B under the same environmental and agent specific conditions described in relation to drug A. Here drug B price follows similar behaviour and shows that the ERP regulation with price calculation on min effect, when prescribing is on brand (scenario 2 and scenario 3), is very much similar with the scenario when there was no ERP, but prescribing is on molecule (yellow diamond line and blue dashed line). This observation means that the above options are interchangeable and policy decision making should be in favour of the one without ERP since it would eliminate possible unwanted ERP induced pricing spillover effects motivating drug market exists. Using ERP regulation with calculation on min when local market prescribing is on molecule can undermine drug availability level up to 66 % possible market exits of all simulated time it could have been present on the local market.

Like in drug A scenario options, here a 'no ERP' policy in a branded prescription market would not be recommendable because it favours highest drug price levels throughout the whole simulated time period. What would be recommendable is that in markets with prescribing on molecule, it would be better not use ERP regulation with calculation on min, but instead utilize and foster market competition on price through providing quicker market access to innovative and generic drug rivals, avoiding the ERP spillover effects and induced drug market exists. On the opposite, in local markets with prescribing on brand, it would better use ERP regulation with price calculation on min in order to increase drug price level of affordability for the public budget and out of pocket spending.

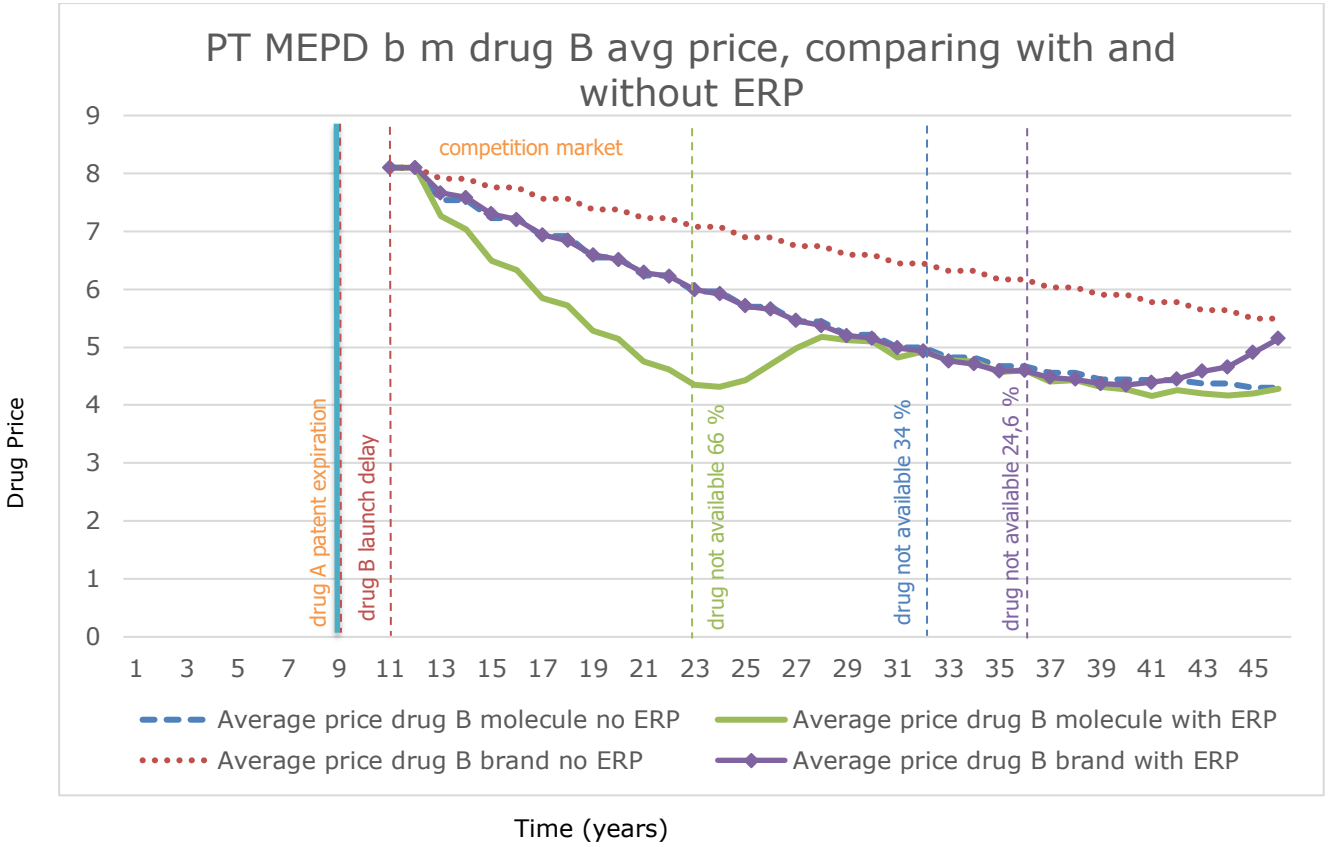


Figure 9.3.10.I.B Comparing statistical means of drug prices from 100 runs for all four scenarios (drug market price discounts are made stochastic): ERP base case from section 9.3.8 for Drug B versus ERP regulation with 'brand' prescribing, 'No ERP' regulation with 'brand prescribing' and 'No ERP' regulation with 'molecule' prescribing

This situation with drug B first entering the generic market, is repeated with its second generic rival drug C (9.3.10.4a, 9.3.10.3.b, 9.3.8.3.I.C) even on a higher extent showing that drug C price affordability level is and stays even higher in a 'no ERP' scenario in a 'molecule' competition market (scenario 3), compared to an ERP market with prescribing on brand (scenario 2).

The three graphs on the price evolution of drug A, B and C are showing that ERP regulation is not an isolated tool and it interferes with local competition, price tactics of pharmaceutical companies and prescribing regulation. It is important to take into account local prescribing regulation and number of drug rivals on the market in designing and adjusting a proper and adequate ERP regulation tailored not only to each local market but also to innovative and generic drugs. Also, ERP could interfere with local requirements for public price discounts, which if leading to a lower price compared to the tactical price threshold of the marketing authorization holder, it could hinder drug market entry or make the drug unavailable due to market withdrawal.

Another effect of the ERP regulation on min when the local prescribing is on molecule is that it could lead to the lowest drug C prices without making it exit the local market, but it is due to drugs A and B going out of the market, due to combined effects of ERP regulation, price competition and prescribing regulation and leaving opportunity for drug C without to utilize the whole market demand without having rival competition.

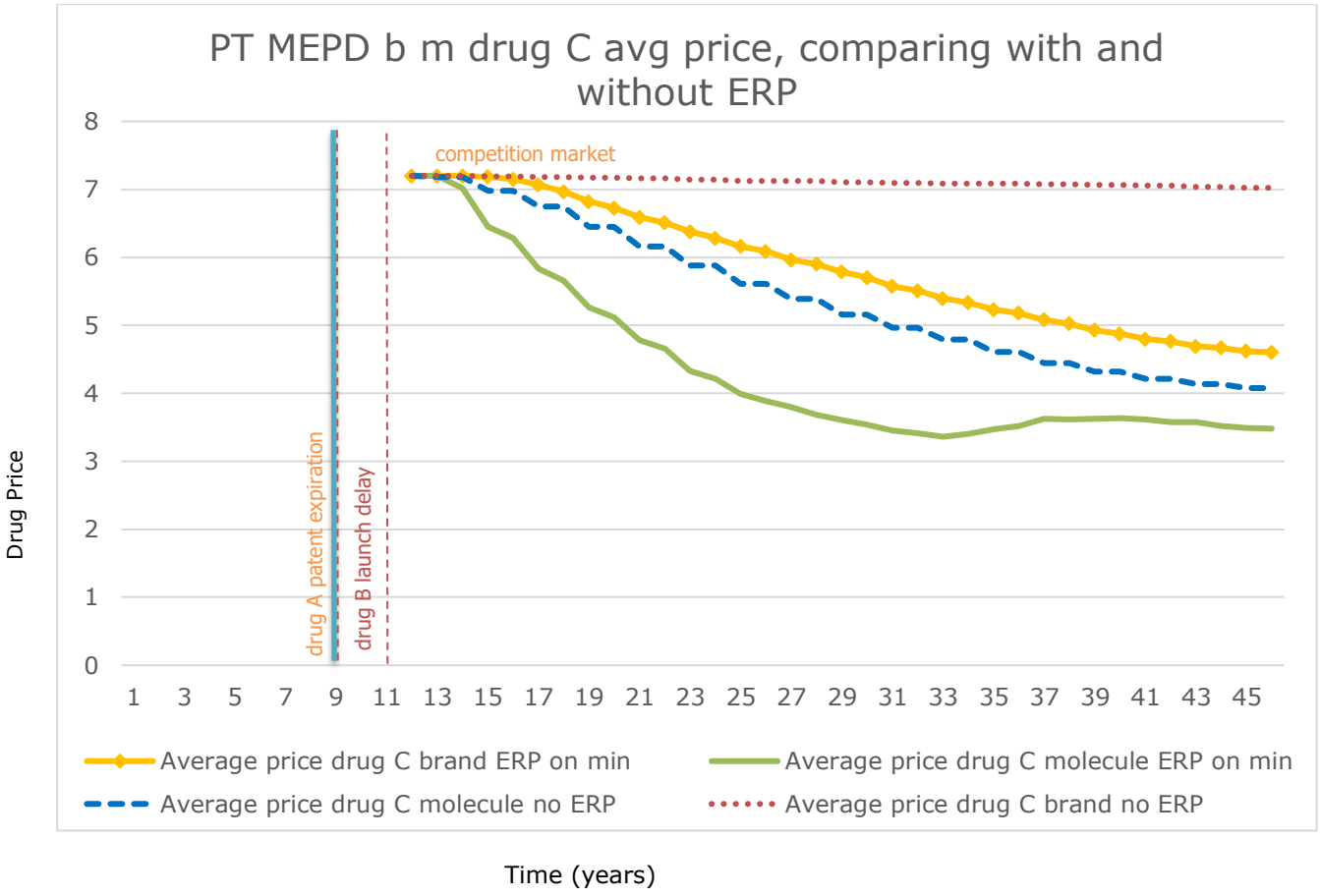


Figure 9.3.10.I.C Comparing statistical means of drug prices from 100 runs for all four scenarios (drug market price discounts are made stochastic): ERP base case from section 9.3.8 for Drug C versus ERP regulation with 'brand' prescribing, 'No ERP' regulation with 'brand prescribing' and 'No ERP' regulation with 'molecule' prescribing

9.3.10.2.C Scenarios on drugs A, B and C price evolution in an ERP market with price calculation on "avg", compared to a no ERP market and local prescribing on brand or molecule variation

The next three graphs on Figure 9.3.10.II.A, Figure 9.3.10.II.B and Figure 9.3.10.II.C exhibit drugs A, B and C price evolution in an ERP market with price calculation on "avg", compared to a no ERP market and local prescribing on brand or molecule variation. Here

the "no ERP" market with prescribing on "molecule" outperform all other policy options, although it could lead to a 64 % and 34 % drug A and drug B withdrawals, but due to price competition and not to ERP regulation.

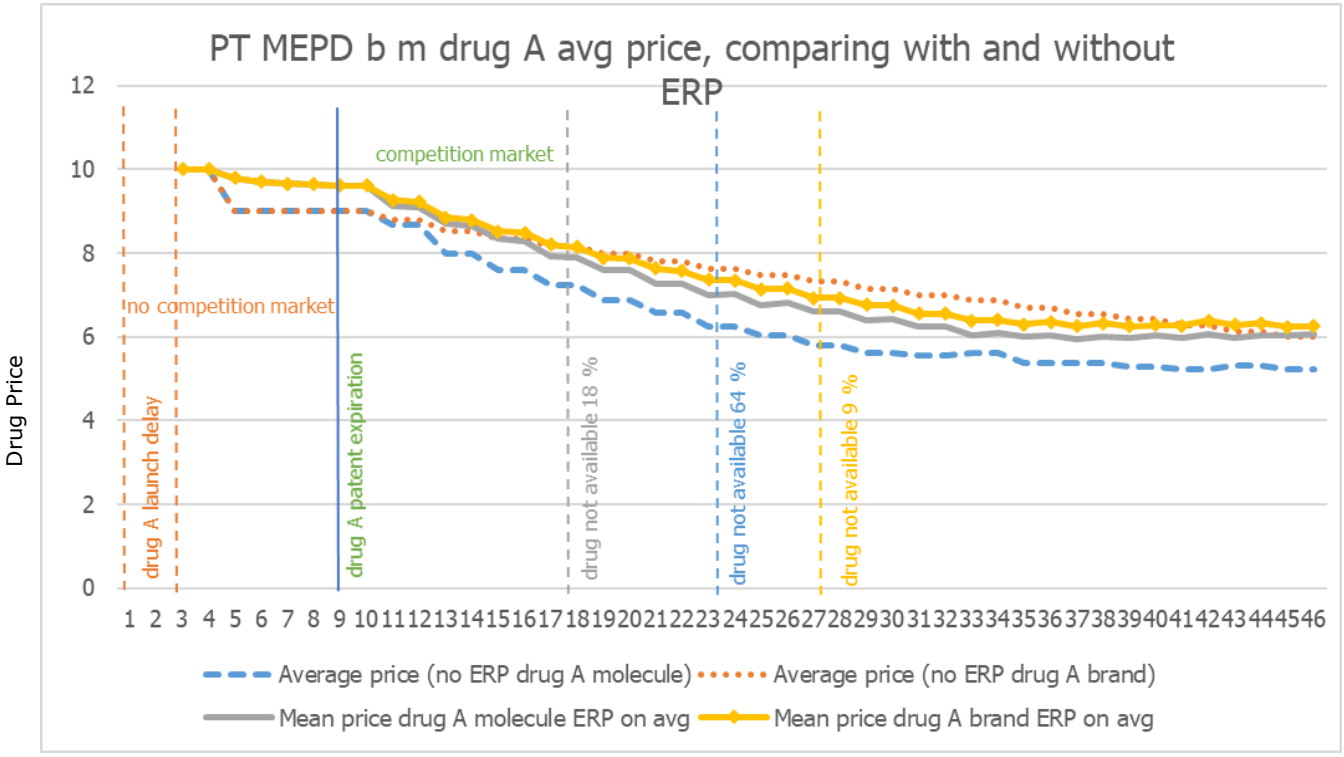


Figure 9.3.10.II.A Comparing statistical means of drug prices from 100 runs for all four scenarios (drug market price discounts are made stochastic): ERP base case for Drug A with price calculation on 'avg' versus ERP regulation with price calculation on 'avg' and 'brand' prescribing, 'No ERP' regulation with 'brand prescribing' and 'No ERP' regulation with 'molecule prescribing

In this scenario, price calculation formula is changed from minimum ("min") price taken out of the reference country basket price of the same drug, to taking the average ("avg") of all prices. Price averaging seems to have a moderate (smoothing) price decrease effect with no abrupt changes in price and no drug exits for the simulated ten year period, compared to the scenario with minimum price calculation.

In this scenario, changing the local prescribing regulation from 'brand' to 'molecule', while the ERP calculation is done on the average and not on the minimum of the reference drug prices, brings a little more to the affordability effect. It is an important outcome, because it provides and insight in the capability of the ERP to compensate for

the differences in the local prescribing regulation in different countries by brand and by molecule, when the ERP calculation is done by averaging the reference drug prices.

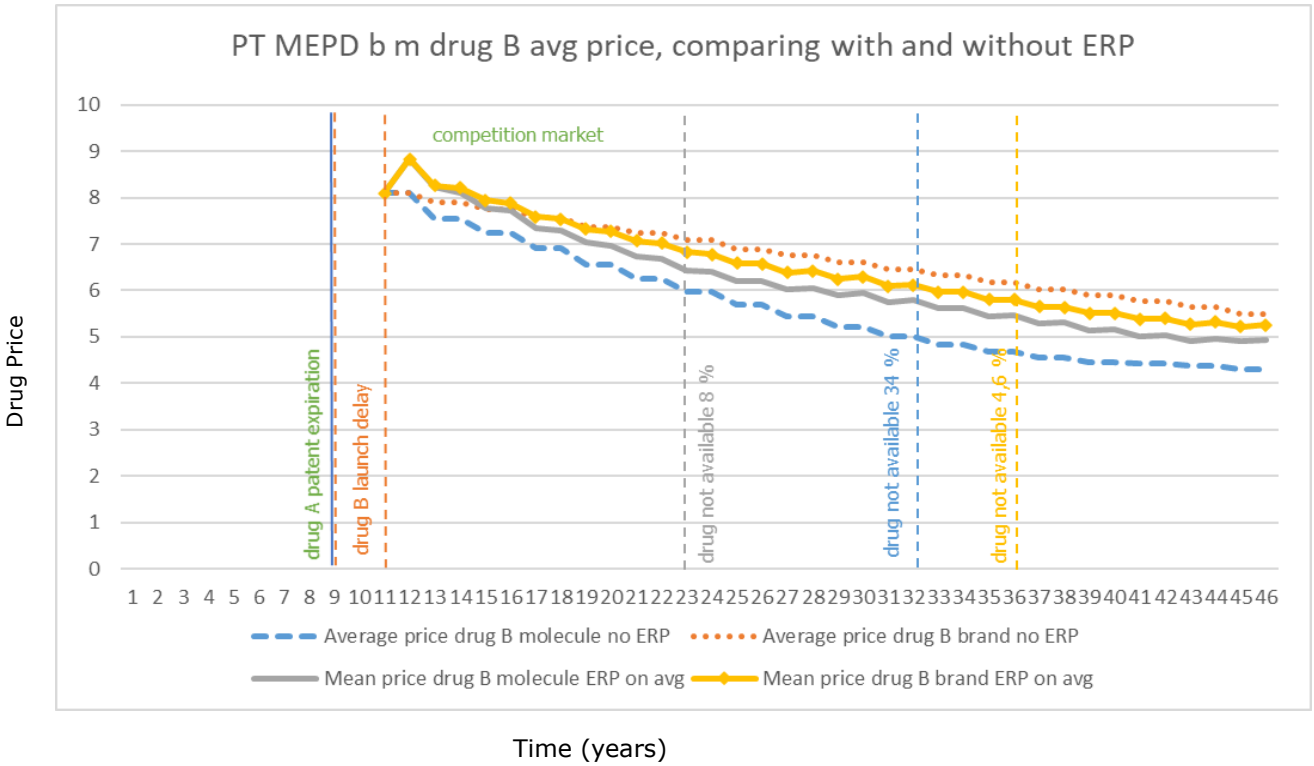


Figure 9.3.10.II.B Comparing statistical means of drug prices from 100 runs for all four scenarios (drug market price discounts are made stochastic): ERP base case for Drug A with price calculation on 'avg' versus ERP regulation with price calculation on 'avg' and 'brand' prescribing, 'No ERP' regulation with 'brand prescribing' and 'No ERP' regulation with 'molecule prescribing

Another favorable effect of this ERP policy scenario is related to the drug availability criterion, since no drug exits occur in the explored local market. However, this does not prevent drug exits indirect effects in any of the rest of the ERP markets

ERP on "avg" policy favors higher drug prices compared to ERP on "min" policy option but on the other side, it keeps unavailability level lower. However, public price state discounts could be not utilized in full or even are neutralized due to the price averaging effects of the ERP "avg" price calculation formula and the combination of reference

basket countries.

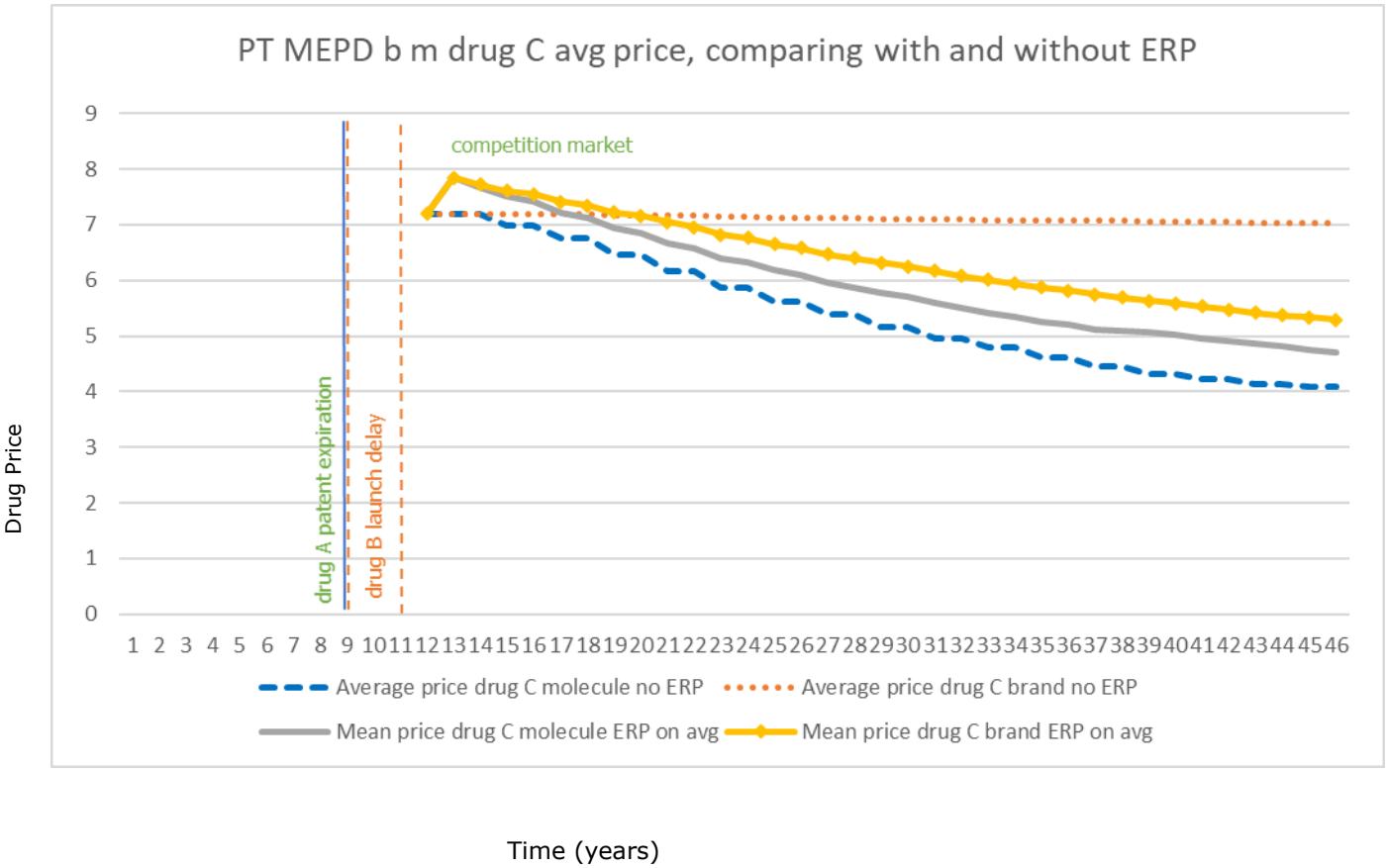


Figure 9.3.10.II.C Comparing statistical means of drug prices from 100 runs for all four scenarios (drug market price discounts are made stochastic): ERP base case for Drug A with price calculation on 'avg' versus ERP regulation with price calculation on 'avg' and 'brand' prescribing, 'No ERP' regulation with 'brand prescribing' and 'No ERP' regulation with 'molecule prescribing

In general, following the observations of the simulated scenarios and policy options, it could be stated with confidence that off patent markets with local prescribing regulation on "molecule" provide more sustainable conditions for achieving higher levels of drug access, availability and affordability without ERP regulation in comparison with other options. However, in markets with local prescribing regulation on "brand", ERP regulation can bring value in relation to all three criteria, especially on affordability of drugs on an "off patent" market. ERP brings no or limited effect on increasing access, affordability and availability of on patent drugs but on the opposite, it could hinder or delay drugs market access and provoke drug market exists, due to reference basket countries price benchmarking avoidance tactic, on one side, but on the other it could support higher on patent drug price transfer around ERP local markets in EU.

9.4 Recommendation for optimal policy decision making

The ERP hybrid simulation is capable of producing more realistic price evolution behavior in comparison to previous ERP DE simulation approach (Toumi et al., 2014), due to introducing agent behavior and resource feedback complexity, representing more accurately pharmaceutical market complex adaptive system characteristics. This way the ERP hybrid simulation is overcoming previous DE simulation limitations related to not taking account of the counter effect of drug manufacturers' market and pricing strategies, parallel trade effects and contextual regulation effects.

The hybrid simulation experiments provided evidence that, for example, in a scenario where ERP regulation remains like it is, but prescribing regulation is changed from brand prescriptions to prescriptions by molecule (fostering market price competition), effect on drug availability (drug market exit) can occur quicker, especially for the off patent innovative high priced medicines. Some generic drugs could also follow suit their exiting rivals due to pricing tactics (Figures 9.3.9.I, 9.3.9.II, 9.3.9.III).

Access would not be affected due to the ERP application. It has been shown that ERP regulation provides a mechanism for price propagation around reference countries and at the point of entry it can be used by drug suppliers to legally transfer their initially registered as high as possible prices in the most attractive (high GDP) reference countries. Access of a medicinal product could be hindered due to other reasons, for example if there were a requirement for a mandatory price discount for publicly reimbursed drugs, or there were a requirement for the entering drug to have been included in public payment schemes in more than one reference countries prior to local public price registration (Figures 9.3.6.1, 9.3.10.I and 9.3.10.II). These conditions are not a part of the ERP rules but could be a state public funding requirement, which changes often and is more a part of the price negotiation procedure than a legal official requirement. For this reason and for the reason of their interfering effect with the ERP regulation, they have been included in the present simulation analysis which is focused on ERP induced effects, interfering with main contextual regulation and parallel trade activities, all affecting market price competition and pricing tactics of the drug suppliers.

Another important observation that is constant among all scenarios presented here, is that any change in the ERP tool box and or change in the local prescribing regulation, including change in parallel trade activity status, leads to changes in price evolution dynamics in the rest of ERP countries in EU (Figure 9.3.4.1, Figure 9.3.5.1, Figure 9.3.9.I, 9.3.9.II, 9.3.9.III). This makes ERP policy crafting very complex and difficult with

respect to achieving health care objectives of equitable access, availability and affordability in the long run, and the ERP effects in one country volatile and directly dependent on ERP and contextual regulation changes in any of the ERP reference basket countries, while indirectly dependent on the rest of the countries using ERP. A counterintuitive outcome also is present, related to the belief that drug prices should converge over time across EU local markets. It can be observed on any of the Figures exhibiting the comparative price evolution in the selected six countries that even prices of the same drug could remain different in different countries (for example, look at the price evolution of drugC in Austria and in Slovakia, maintaining the highest price at the end of the simulated period in the first, and the lowest price in the latter country market, Figure 9.2.1.4, 9.2.1.5 and 9.2.1.6)

Main general insights, coming out of the scenario simulation results:

- ERP alone has no effect on drug access delay, instead it provides an attractive route for propagation of the highest price of the first country of launch to other referencing countries.
- Other factors like mandatory official price discounts for inclusion in a country's reimbursement list or a requirement for a drug to be included in a predefined number of reference countries reimbursement list, can have effects on delays in local markets, which could interfere with the ERP rules;
- ERP alone has no price decrease (affordability) effect for on patent drugs or any drug in a monopolistic market (if there are no other price decrease mechanisms, like drug price competition or mandatory price discounts);
- Price decrease is an effect mainly from local price competition intensity, which ERP regulation only transfers to other reference basket countries, which can lead to a faster price decrease reinforcing feedback effects in some of the countries, depending on reference price calculation (minimum or average) and reference country basket composition variation;
- ERP has effect on drug market exits (level of availability) for off patent and generic medicines, depending on individual pharmaceutical firms' profit margin thresholds and on the indirect effect of price competition, local prescribing regulation and parallel trade in reference basket countries;
- Due to the fact that ERP regulation parameters, contextual prescribing regulation and competition differ for each country, effects on drug access, affordability and availability level could be higher, moderate or lower in different local markets and finding optimal combination of ERP parameters for a country needs to follow a carefully configured parameter variation or optimization (to perform an optimization search of all possible variations for one country reference basket only

of 10 countries out of total number of 30 countries, N = 30, K =10, approximately 30 million combinations should be tested by simulation, without including combinations with other variables);

9.4.1 Main recommendations

Main recommendations are made here in connection and comparison with previous key recommendations in published recent research, regarding the ERP effect on the pharmaceutical market systems (Table 9.4.1). Main insights coming from the hybrid ERP simulation analysis regarding key criteria of ensuring drug access, affordability and availability are presented in Table 9.4.2.

Table 9.4.1 Main ERP Policy Recommendations

Publication	Insights from relevant publications on ERP effects on the market	Limitations in published research on ERP	Hybrid ERP simulation insights in comparison to previous research
WHO guideline on country pharmaceutical pricing policies. (2015). World Health Organization	Countries should consider using ERP as a method for negotiating or benchmarking the price of a medicine. Countries should consider using ERP as part of an overall strategy, in combination with other methods, for setting the price of a medicine. Countries/payers should select comparator countries to use for ERP based on economic status, pharmaceutical pricing systems in place, published actual versus negotiated or concealed prices, exact comparator products supplied, and similar burden of disease	Claims have been made that ERP has been effective in reducing the prices of medicines. However, the policy review found no supporting evidence from monitoring reports or rigorous analytical studies. The underlying assumption justifying the use of ERP is that prices in reference countries are somehow right, appropriate, or fair and thus by definition the ERP derived local price structure will also be appropriate. This assertion is clearly very difficult to assess without objective criteria.	ERP is a tool to transfer public prices among reference countries, which remain higher than actual market prices and provide a mechanism for companies to propagate their highest possible prices legitimately among reference countries (Figures 9.3.6.3 and 9.3.9). For the above reason, companies do not have incentive to delay their launches, but on the opposite. If delays occur, they are connected to countries with official discount requirements for public financing which can interfere

			with the ERP among reference countries (Figures 9.3.4.a, 9.3.10.I and 9.3.10.II). Market exits can occur if a drug price reaches a predefined threshold in connection to avoidance of ERP spillover effects or target profit margin erosion (Figures 9.3.7, 9.3.9, 9.3.10).
II. Vogler, S., Lepuschütz, L., et al., 2015. *Study on enhanced cross-country coordination in the area of pharmaceutical product pricing - Final Report*	In designing EPR, policy-makers should carefully decide on the **methodology** in line with the underlying policy objectives and principles since methodological specifications can have a major impact on the effectiveness of EPR, in particular with regard to the potential of savings to be generated.	EPR was the only price determining criterion, ignoring other aspects such as negotiation, thus the model did not incorporate all aspects affecting medicine prices; No volumes or demand elasticity information and thus can only provide judgements on price developments, but no conclusions	The limitations of the static simulation are overcome by the hybrid ERP simulation, because it includes pharmaceutical companies pricing and competitive behaviour and how it interferes with the ERP effect (Chapter 8 and Chapter 9). Also, sales volumes and demand are included in the hybrid ERP simulation which have effect on

	In this context, policy-makers are advised to ensure the performance of price monitoring at regular intervals, with subsequent **price revisions** Policy-makers should consider referencing to **discounted prices** instead of list prices. Since the disclosure of confidential prices is highly politically sensitive and might not be feasible in the short-term, Member States might consider in a first step to reference to officially published discounted prices (statutory discounts), and to elaborate strategies, together with other countries, about a possible consideration of confidential discounts	on changes in turnover or overall savings of different stakeholders The model is static in nature, i.e. considers the development of prices under certain defined country attributes and policy rules. Dynamic effects, such as companies reacting to lower or higher profits, or countries adapting their rules based on overall spending, are not incorporated. This is relevant since, as is discussed in this report, pharmaceutical industry may respond strategically to EPR schemes. These limitations mean that model results need to be interpreted carefully. The model aims at illustrating the workings of current EPR systems and the impacts of different methodological changes; it was, however not designed to perfectly predict medicine prices.	companies' market share and competitive tactics. All above extended capabilities provided for more credible simulation results. The ERP can be exploited to the benefit of companies rather than to the benefit of budget payers and price authorities (see simulation scenarios experiments in Chapter 9). In the above respect timing of price revisions can have effect on the quicker or slower price reductions and price convergence. Also, ERP price calculation formula and reference countries baskets differences can have effects on price reduction evolution (Figure 9.3.10).

	Policy-makers should carefully consider the selection of the **reference countries** from similar economic status in relation to savings and access		If real market prices including discounts are taken into account in the ERP tool, this could lead to drugs unavailability and drug exits (Figures 9.3.10.I, 9.3.10.II, 9.3.10.III). ERP is a tool which effects in practice can be either exploited or avoided by companies.
III. Toumi, M. et al., 2014. External reference pricing of medicinal products : simulation- based considerations for cross- country coordination Final Report	ERP considered as an isolate pricing rule can lead to lower drug price erosions, than what could be observed suggesting that other pricing policies, potentially amplified by ERP, are involved in driving prices down. Timing for price revision, reference price calculation	Did not take into account of important market and regulatory contextual factors and cannot produce credible results and analysis: o No parallel trade interfering effect o No drug companies' tactic in response to the ERP	A hybrid SD and ABM approach can support simulation experimentations including not only pharmaceutical companies pricing, marketing, launch and exit tactics, but also parallel traders, showing that their effect further increase price and market share competition (Figures 9.3.1.1 to 9.3.1.4;

	method, reference countries basket, reference price source and generic competition are main components of the ERP rules having effect on price decrease.	○ No price or marketing budget competition among companies ○ No prescribing and buying behaviour ○ No other local pricing and prescribing or dispensing regulation interfering effect with ERP	9.3.2.1 and 9.3.2.2; 9.3.3.1 and 9.3.3.2;) Also, such approach can support simulated experiments with local contextual regulation, like INN (MOLECULE NAME) or brand prescribing and buying behaviour, and showed that the INN prescribing intensifies price competition while brand prescribing keeps prices on a higher level for longer time (Figures 9.3.10.I, 9.3.10.II, 9.3.10.III). Since ERP is a price benchmarking tool, it can only transfer official registered public prices among referencing countries (see simulation scenario experiments in chapter 9).

IV. Fontrier, A., Gill, J. & Kanavos, P. International impact of external reference pricing: should national policy-makers care?. *Eur J Health Econ* **20,** 1147–1164 (2019)	ERP appears to be associated with international implications, including spillover effects, price instability, price convergence and launch delays; ERP effects cannot be solely attributed to or caused by ERP and there are other factors at play, like market size and income levels, and other supply-side regulations; all these can either amplify or reduce ERP impact. ERP cross-country implications are well known to decision makers, and need to be considered in the design of ERP rules	Given that the evidence we found in the currently available literature was mostly weak in terms of quality and derived mainly from grey literature, the above observations should be interpreted with caution. Importantly, there seems to be a dual unmet need: the first, relates to what constitutes an optimal ERP system design, so that its impact across countries would be at least neutral; and, the second, relates to the robust quantification of its impact at international level, including practices countries have used to address spillover effects	Hybrid simulation scenario experimentation showed that the resource agent approach can help decision makers in their optimal search for a sustainable ERP and can help for the proper evaluation of the ERP international effects. It also proves the hypothesis that spillover effects, price instability and price convergence or divergence, and launch delays, cannot be connected only to the ERP, but to the interfering effects with local contextual factors like competition and other related regulations that are having influence on the supply and demand of medicines (see all scenario simulations in chapter 9).

Holtorf, A. P., Gialama, F., Wijaya, K. E., & Kaló, Z. (2019). External Reference Pricing for Pharmaceuticals—A Survey and Literature Review to Describe Best Practices for Countries With Expanding Healthcare Coverage. *Value in Health Regional Issues*, *19*, 122-131	Directly related to ERP Scope: Reimbursement of single-source products (on-patent pharmaceuticals); Composition of country basket: Select 5-7 countries with similar socioeconomic and HC environment; Price calculation: Calculate the average or median price of the same product; Frequency of price revisions: Not more than yearly or biannual and allow reasonable time for implementation; ERP should be part of a comprehensive pharmaceutical policy	The paper recommendations reflect pharmaceutical industry pricing experts experience The research is supported through a pharmaceutical firm grant	ERP has no price reduction effect on patented or other drugs in a monopolistic market (Figures 9.3.10.I, 9.3.10.II, 9.3.10.III). ERP can have price reduction effect if it refers to market competitive prices, but due to the above, it can lead to unavailability effects following drug market exits or refraining of local launch (Figure 9.3.9.I, 9.3.9.II, 9.3.9.III). Composition of reference countries basket (Figure 9.3.5.1), price calculation formula and timing of price revision (Figure 9.3.9.I, 9.3.9.II, 9.3.9.III) can have effects on the level of prices, time of access and unavailability of medicines.

Maini & Pammoli 2020	External reference pricing (ERP), generates an incentive for firms to withhold products from low-income countries. ERP increases entry delays in eight low-income European countries by up to one year per drug	The paper undertakes a historical approach on pharmaceutical firms behavioural effect of the ERP regulation, but does not include scenario analysis nor interfering effects of contextual regulation (prescribing or reimbursing) and parallel trade.	This analysis confirms the hybrid SD&AB scenario exploration in relation to drug access (delays in countries with lower GDP index)
Geng & Saggi 2017	In a two-country (home and foreign) model, home's unilaterally optimal ERP policy permits the home firm to engage in a threshold level of international price discrimination above which it is (just) willing to export.	The paper limits its analysis to one on patent drug manufacturer decision behaviour and two countries, not taking into account larger number of countries, competition and contextual regulation, nor parallel trade interfering effects.	The results confirm the hybrid SD & AB scenario simulation experiments on drug unavailability due to min. 'threshold' price tactics.
Geng & Saggi 2020	In a two-country (home and foreign) model, the home producer of a branded pharmaceutical product faces generic competition in each market. Home's nationally optimal ERP policy lowers domestic price while	The paper limits its analysis to one on patent drug manufacturer behaviour and two countries, not taking into account larger number of countries, including only one rival generic pharmaceutical firm, but not evaluating contextual	The results confirm the hybrid SD & AB scenario experiments in relation to the 'spill over' effect of high prices from first country of launch to the rest of the country markets.

	maintaining the firm's export incentive. This ERP policy results in a negative international price spillover that the foreign country can (partly) offset via a local price control	regulation, nor parallel trade interfering effects.	

Table 9.4.2 on hybrid ERP simulation insights and recommendations for decision makers

Criteria	Recommendations	General notes connected to all three criteria and provided recommendations
Ensuring equitable access	ERP application should not interfere with local official discount or other price reduction tools, otherwise it could incentivize companies to refrain or delay launch in given local markets (Figures 9.3.6.1, 9.3.10.I and 9.3.10.II) Countries baskets should better include a broad number and variety of markets, to avoid drug entry delay (Figures 9.3.6.2)	ERP could be more effective if applied as a regular supporting tool for price negotiation and price setting, rather than just a price setting tool. This will enhance the bargaining power of public payers to achieve affordable prices relative to countries budget without hindering equitable access and product availability in local markets Reference basket countries should be tailored to the ERP applying country market, for example, markets having lower level of competition should refer to more competitive markets within the EU, in order to take benefit of the more matured markets and to offset its weak bargaining position (Figure 9..5.1) In relation to price calculation formula, countries with less competition should refer to minimum prices, while countries with more matured competitive markets could refer to average prices (Figure 9.3.10 regarding differences between ERP on "min" and ERP on "avg")
Ensuring price affordability	ERP should be used as a price negotiation and price setting supporting tool for achieving prices affordable to the local payers, and further for price benchmarking revisions and price renegotiation ERP tool box (drug price calculation formula, time period revision, reference basket countries, prescribing on "brand" or on "molecule") should be configured to the local payor objectives (Figures 9.3.10) Application of ERP to on patent drugs or off patent drugs on a monopolistic market, without using other pricing tools and local	

	discounts for reimbursement, could be misleading because price benchmarking can be used for high price propagation (Figures 9.3.6.4 and 9.3.10.) ERP should take into account local price competition and real market prices for the purpose of effective price negotiation and renegotiation for public payers (Figures 9.3.10.I, 9.3.10.II, 9.3.10.III)	Regarding timing of price revisions, countries with less competition should review prices in shorter time periods than countries with intensive competition (Figures in section 9.3 on EU wide simulation experiments) ERP application should take account of parallel trade effects and effects of local pricing, prescribing, dispensing and reimbursement regulation, which alone or in combination can have indirect amplifying or reducing influence on the ERP effects on drug access, price affordability and availability (Figures 9.2 and 9.3.10 regarding prescribing on "brand" or on "molecule", 9.3.7, 9.3.8 and 9.3.9) Local pricing authorities should consider using simulation tools in order to enhance their capabilities for ERP tool box scenario exploration in combination with local contextual market factors and medicines regulation and to improve their decision making in relation to their objectives and key criteria for equitable access, affordability and availability (Figure 8.6.5.4, 9.2.1 and 9.3.6 on user dashboard versions for scenario simulation experimentation and analysis)
Ensuring medicines availability	ERP application should take account of market exit tactics due to price decrease spillover effect but only for single market molecules (Figures 9.3.7, 9.3.9, 9.3.10) In a competitive market there are other competitors supplying the same molecule which can ensure a given medicine availability even if one of the competitors makes decision to exit a local market (Figures 9.3.9 drug C and 9.3.10 drug C)	

The above simulation analysis and policy recommendations regarding the ERP regulation evaluation, are related tightly to the "Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States" (Council of the European Union 2016) and provide new knowledge on the ERP effect on equitable drug market access, drug affordability and drug availability. The ERP simulation took account of companies pricing and marketing strategies in response to the local ERP and the outcome showed the ERP is not an effective tool in reducing market prices. ERP functions more in favour of pharmaceutical companies than of pricing authorities and it must be used for initial benchmarking of the ceiling price of a medicine, after which price negotiation can follow according to local country objectives and requirements. ERP is deceptively perceived to be an effective price containment tool, but instead it propagates inflated public prices among referencing countries while real market prices remain unaffected. When ERP is interfering with other price reduction mechanisms like market competition or price discounts, it can propagate both upward or downward changes in public prices.

In the above respect, ERP would either remain ignorant for the real price competition or could propagate its effects to a point when high prices persist among ERP countries, or drug exits occur. In best it can be applied like an initial price reference negotiation tool followed with price negotiation aiming at reaching a lower unofficial price for reimbursement than the min official public price in the reference countries basket. This policy evaluation showed that the ERP regulation can affect the price affordability of medicinal products in both upper and lower directions, and can have indirect effects on both innovative and generic drugs unavailability and launch delays. Also, the simulation analysis demonstrated that pharmaceutical companies can respond strategically to exploit or avoid this regulation. This presented clear evidence that the ERP regulation can provide "possible unintended or adverse consequences of incentives" which could undermine the sustainability of national healthcare systems.

The ERP hybrid simulation analysis presented here can further be improved by broadening its scope including more contextual regulation like, Internal Reference Pricing in reimbursement groups made by drug molecule or by therapeutic groups, levels of public reimbursement, time delays due to market authorization and price registration procedures and other. Furthermore, the ERP hybrid simulation is capable of configuring parameter variation experiments for the evaluation of outcome sensitivities to a chosen group of input parameters, and of constrained optimization which can help to find optimal configuration of system variables for the minimization of the ERP counter effect on equitable access and availability, and maximization of its effect on affordability of medicinal products

Chapter 10 Contribution of PhD research and future research implications

10.1 Contribution of PhD research and future research implications

Parts of Chapter 10 include text from the above published journal paper, coauthored with professor Susan Howick and professor Alec Morton (Kazakov et al., 2021), specifically from section 11 of the paper.

My PhD project purpose was to evaluate ERP regulation in EU from the perspective of main healthcare objectives of providing equitable access, availability and affordability of drugs on local EU country markets. This purpose informed the main research question of my PhD project: What is the effect of the ERP regulation on equitable access, availability and affordability of drugs in EU.

To explore and provide answers to my PhD research question, I have developed first an integrated RAM framework as a novel PSM to aid resource/agent complex system analysis. This has been possible through the support of resource/agent related theories such as Resource based Theory, Resource Dependence Theory, Behavioural Decision Theory and Anticipatory Systems Theory, which provide rich perspectives on the comprehensive management of complex adaptive systems, sustaining a theoretical framework supportive of resources and agents interdisciplinary conceptualisation and practical integration.

The development of the enhanced RM and the novel AMs and their hybridisation in a RAM were motivated in three ways:

(i) researchers identifying the needs of future PSMs, to take account of interdisciplinary perspectives, borrowing theory and developing procedures for integrating different modelling methods (Ackermann et al. 2014).
(ii) the application of agent based, and resource-feedback approaches have traditionally been carried out from the individual perspectives of resource structure or agent behaviour. These are opposing macro/micro, and resource/agent perspectives. The lack of a joint conceptual/qualitative hybrid model building procedure led to calls for hybridisation of both of these perspectives (Guerrero et al. 2016; Scholl 2001; Schieritz 2002).
(iii) a need to maintain a "comprehensive perspective" (Rosenhead 2006) of complex adaptive systems (combining both resources and agents views)

In accordance with the key challenges of borrowing and developing theory and developing a conceptual framework and procedure for combining different methods (Ackermann et al. 2014; Howick & Ackermann 2011), key contribution of my PhD is to combine resource related theories with agent behavioural related theories, and to develop a novel RAM problem structuring approach which can maintain a "comprehensive perspective" (Rosenhead 2006) to complex adaptive systems.

The PhD thesis demonstrates also how RM method can be enhanced through adding an external resource perspective, thus taking account of external resource dependence, through the Resource Dependence Theory. The newly developed AMs (AiM and AbM techniques) provide a means for capturing agents ''cognitive structure" (Anderson 1999; Macal & North 2015) and fill a gap in AB modelling practice, related to a lack of a conceptual modelling approach, through bringing in Behavioural Decision Theory and Anticipatory Systems Theory. Furthermore, this can aid conceptualization and validation (Heath et al. 2009; Klügl 2008; Kasaie & Kelton 2015) through visualisation of agents' cognitive structure in the form of an "if/then" condition action map, depicting agents' actions and the conditions they depend on.

Combining AM and enhanced RM into a hybrid RAM method can provide a comprehensive resource agent perspective to complex adaptive system research by capturing agents' behaviour related to system resources, and their interrelations. Application of the RAM framework can also provide insight into the key "turning points" in the system subjected to the effect of the agents' adaptive behaviour. Placing the RAM framework within the different resource and agent theories can ensure its theoretical and methodological consistency. From a mixing methods perspective, the RAM approach also provides a theoretically sound and structurally robust methodological procedure for mixing SD and AB modelling and simulation.

In addition to designing a novel problem structuring method, RAM can also be used as a hybrid qualitative conceptual modelling procedure for resource and agent interactive systems such as pharmaceuticals and health care. Conceptual modelling is acknowledged to be a key tool for model validation and confidence building in health care and aims to help the structural modelling and validation (Roberts et al. 2012) procedure. Validation and confidence building focuses on the correspondence between the real world phenomenon under examination and a simulation model (Marshall, Burgos-liz, et al. 2015) in an iterative, transparent and visualised process. (Law, 2009) This aims to ensure qualitative and quantitative (Eddy et al. 2012) consistency between the real world and a simulation. A hybrid RAM can strengthen the integration process between the resource and agent modelling approaches, and confidence building among modellers and

users (Howick et al. 2008; Macal 2010), by applying it as a joint conceptual modelling procedure. This ensures that the qualitative modelling stage is theoretically and methodologically consistent with a quantitative simulation modelling phase.

The RAM application to the ERP regulation evaluation provided a means for rich scenario identification, and for a consistent and robust procedure for hybrid scenario simulation exploration in relation to the PhD research question. Further in the second stage, it has been used for the design and building of a hybrid SD and AB scenario simulation model and into a public policy scenario simulator for scenario testing and experimentation (including parameter variation), capable to support comprehensive ERP policy evaluation and decision making. This scenario simulation building stage was implemented into a Anylogic software environment, but the RAM procedure for hybridisation of SD and AB perspectives can be used for and can support implementation in any other software, providing such technical capabilities (like for example, Repast Symphony, Olafsdottir, et al (2019)).

The ERP qualitative and quantitative analysis demonstrates that applying a RAM approach can enable a comprehensive evaluation (taking account of both resource-feedback and agent-based perspectives) of the ERP effect on drug equitable access, affordability and availability. It can also produce a rich picture of the market dynamics, and can provide problem structuring insights, including scenario generation and identification of possible system improvement interventions. In addition, the analysis extends previous research on the ERP, helping to overcome previous limitations (Toumi et al., 2014, Vogler et al. 2015). Scenario identification and experimentation can therefore support policy making to improve the ERP regulation by introducing changes aimed at offsetting the effect of the regulation on drug access delay, unaffordability and unavailability in EU local markets

My PhD main contribution is connected to both methodological and practical aspects of developing a novel problem structuring method (RAM) and using that method as a conceptual validation and hybridization procedure for designing a hybrid simulation for the evaluation of a practical healthcare policy questions regarding the ERP regulation effects on the pharmaceutical market system in EU.

The methodological and theoretical contribution emerged from the necessity of the development of a suitable problem structuring and qualitative modelling theoretical framework and method, needed for the practical exploration and analysis of the ERP regulation in EU in relation to its effects on the key criteria of drug equitable access, availability and affordability on local markets. In addition, the RAM was used as a procedure for integrating SD and ABM methods for hybrid quantitative modelling and

simulation analysis of the ERP effects. Theoretical and methodological contribution came out of bringing together a number of resource and agent related theories in a novel framework for the support of the RAM method development and application.

The practical contribution to health care and drug policy evaluation is connected to the qualitative analysis of the ERP market effects using the RAM framework, to the quantitative analysis of the ERP regulation using a hybrid System Dynamics and Agent based simulation and to the development of an ERP policy scenario simulator for drug pricing policy evaluation and decision making improvement, for use by policy decision makers.

The practical benefits further provide rich evidence on the ERP regulation effects which overcome the limitations of the previous DE simulation and extended the analysis of the regulation with a hybrid simulation approach, in support to public policy decision makers. The RAM qualitative and quantitative approach proved capable of including in the ERP evaluation analysis the market agents behaviours (drug manufacturers, parallel traders, pricing authorities and buyers) and contextual regulation factors (prescribing and reimbursement regulation), including resource flows of supplied and consumed drugs in terms of volume and value, as outlined in Tables 9.4.1, 9.4.2 in section 9.4.

Designing and using a comprehensive simulation treatment of the ERP effects from a resource agent perspective, provided means for a better aligned and correct representation of the real ERP system endogenous components and interrelations, which supported the comprehensive exploration of the main research questions, related to the ERP effects on the access, affordability and availability of medicinal products.

10.2 Limitations and Future Research

The resource agent mapping approach proposed here represents a more complex method than applying methods that only take a resource or agent perspective. It will therefore require more time and expert capabilities to safeguard against errors. However, due to its comprehensive appreciation of a complex adaptive system, involving both resource and agents' interconnections, the hybrid mapping approach can compensate for the limitations of applying only one method, which may neglect important interconnections between system elements. In relation to the above, the more complex theoretical framework applied, although providing richer analytical apparatus, would require prior knowledge of the main theoretical principles that are guiding the RAM methodological

application. This could be a barrier to the proper application of the approach, and thus may require user guidelines to be designed.

Another limitation can be related to the theoretical framework guiding the construction of RAM. For example, other resource and agent decision making theories can provide further valuable aspects, which could need to be taken into account in the RAM design and use. The RAM theoretical framework, being a novel one, has had limited application, which provides not enough practical evidence for its effectiveness evaluation. Another issue which need to be taken into account is related to the specific theoretical (interdisciplinary) knowledge requirements needed for its proper support in the application of the RAM method. For these reasons, difficulties could be associated with its understanding and application both from the perspective of the simulation modelling experts, and from that of the stakeholders that will be the users of the RAM framework insights and analysis.

The RAM method can be further applied in other fields of research, like in sustainable development, agri-food value chains, behavioural and ethics perspectives and other, in order to expand its application and test its usefulness in different domains and settings. This method can be applied also as a participatory modelling framework and to facilitate group model building either in person or in online workshops. Also, relevant aspects of resource and agent related theories can be explored with the purpose to bring higher credibility and consistency with the method purpose and goals.

There are also limitations connected with the simulation analysis of the research question, for example, constrained boundaries and scope related to input data and system parameters, limited interactions between resources and agents, limited selection of simulation experiments and output performance variables, constrained user dashboard features.

Future research can be done to overcome the above limitations and to expand the ERP public policy simulator boundaries, in order to include other relevant global and local contextual factors, influencing resources and agents' behaviour and further elaborate agents' strategic and tactical behavioural routines in relation to pharmaceutical companies and drug regulation authorities.

Such global and local contextual factors can include EU wide and local market regulation applicable to drug pricing and reimbursement, drug prescribing and drug dispensing, differences between on and off patent drugs regulation, other regulations connected to pharmaceutical companies pricing and marketing activities and information provided to

doctors, pharmacists and patients and other topics like drugs overprescribing, drugs public budget management and planning, and other. Also, future research can include application of the RAM qualitative and quantitative methodological framework to other important public policy domains in healthcare, food systems, energy and climate, financial regulation and sustainable economic development, and other.

Appendix A

Table 1.4.1 Appendix A Relevance of Council Conclusions on Strengthening the Balance in the Pharmaceutical Systems in EU to the ERP regulation evaluation

Council Conclusions on Strengthening the Balance in the Pharmaceutical Systems in the EU and its Member States	**Relevance to External Reference Pricing (ERP) exploration and evaluation**
"possible unintended or adverse consequences of incentives and the lack of leverage of individual Member States in negotiations with industry";	Examine if ERP practice could lead to unintended drug entry delay, high pricing and exit of product out of a country market; and to lack of leverage for local government to negotiate lower product price due to circular EU country wide price referencing
"affordability of medicinal products related to high prices";	Examine if ERP could counterintuitively lead to higher pricing contrary to the intention for downward price convergence in EU
"examples of market failure in a number of Member States, where patients access to effective and affordable essential medicines is endangered by very high and unsustainable price levels, market withdrawal of products that are out-of-patent, or when new products are not introduced to national markets for business economic strategies and that individual governments have sometimes limited influence in such circumstances";	Examine if ERP could lead to market failure in any given EU country (explained in the quote on the left)
"functioning of the pharmaceutical system in the EU and its Member States depends on a delicate balance and a complex set of interactions between marketing authorisation and measures to promote innovation, the pharmaceutical market, and national approaches on pricing, reimbursement and assessment of	If the ERP control outcome could be related to the EU wide concern that the pharmaceutical system in EU might be imbalanced regarding (explained in the quote on the left)

medicinal products and that several Member States expressed concerns that this system may be imbalanced";	
"sustainability of national healthcare systems, which may be linked to a number of potential factors, for example the affordability of medicinal products related to high prices, possible unintended or adverse consequences of incentives";	If ERP could have effect on the sustainability of national healthcare systems
"analysis of the impact of the incentives in these EU legislative instruments, as implemented, on innovation, as well as on the availability, inter alia supply shortages and deferred or missed market launches, and accessibility of medicinal products, including high priced essential medicinal products for conditions that pose a high burden for patients and health systems as well as availability of generic medicinal products";	If ERP could have effect on availability and accessibility of innovative and generic products, including high priced essential medicinal products
"Where relevant, the analysis of impacts should also address - inter alia - the development of medicinal products and the effects of the pricing strategies of industry in relation to these incentives;"	If ERP could have effect on the development of medicinal products and on the pricing strategies of industry

Appendix B

Table 2.2.1 Appendix A Literature Review on Pharmaceutical Pricing Policy and Regulation

Publication	Pharmaceutical Pricing Policy and Regulation	SD	AB	Other
Kazakov and Petrova (2015)	Evaluation and impact assessment of what-if policy decisions related to level of product price co-payment and reimbursement of ACE inhibitor on health outcome and public pharmaceutical expenditure	✓		
Li et al., (2014)	Analyzing unreasonably high prices of drugs and the high level of pharmaceutical fees relative to the medical costs of patients	✓		
Zhu et al. (2006)	High medicine price, price fixing due to doctor induced demand	✓		
Homer et al. (2004)	Chronic care program expenditure evaluation (pharmaceutical component)	✓		
Atella, V. (2000)	Minimum reference price policy long-run effect evaluation on drug expenditure containment, drug demand			Econometric modelling
Weinstein et al. (2001)	Analytical framework for evaluating the role of modelling for DM in health and efficient drug utilization			Analytical
Kunc and Kazakov (2013)	Predictive evaluation of pharmaceutical policy component mix (time to market of new generic medicine, product co-payment level, incentivizing generic prescription) and pharmaceutical public expenditure	✓		
Li et al. (2016)	Chronic health clinical and policy relevant analytical review and recommendation for future work in CVD to include modelling the effect of drug therapy		✓	

Greer, A. (2015)	Drug (vaccine) timely availability	✓		
Diaz et al. (2015)	Evaluation of efficient policy planning of resources and capacity for Asthma treatment (drug expenditure)	✓		
Abu Khousa et al. (2014)	Supply chain management in health, drug availability and optimal allocation		✓	
Guertin et al. (2011)	Angiotensin-receptor blockers restricted access economic impact evaluation, drug price			Monte Carlo
Tian et al. (2016)	HT control and treatment intervention for stroke prevention planning	✓		
Lich et al. (2014)	Stroke prevention through hypertension and anticoagulation treatment in Veterans with prior cardiovascular disease and diabetics	✓		
Pombo_Romero et al. (2012)	New drug introduction and planning of pharmaceutical expenditure		✓	
Keshtkaran et al. (2015)	Prevention, treatment, and rehabilitation of stroke (Review)	✓	✓	MCDM and DE
Tang et al. (2014)	Coronary heart disease (CHD): underuse of low cost, high benefit therapies (e.g. beta blockers and statins) and overuse of high cost, low benefit therapies (e.g. elective percutaneous coronary interventions); Health and economic effect of changing financial incentivizing (out-of-pocket expenditure)		✓	
Vila-Parrish et al. (2008)	Inventory and ordering policy for perishable drugs in the setting of an inpatient hospital pharmacy; patient demand; drug unavailability; shortage cost, outdating cost (expirations) and holding cost			Markov chain / MDP
Pasdirtz (2009)	Drug promotion control and pharmaceutical pricing intervention, market failure			State space models

Koppenhaver (2009)	Drug allocation, level of drug shortages, WHO policy performance gap			Mathematical simulation
Vernon et al. (2005)	Pharmaceutical pricing, planning for price regulation			Mathematical modelling
Toumi et al. (2014)	External reference pricing policy (regulation)			DE
Dormuth et al. (2005)	Drug policy initiative financial impact evaluation, out-of-pocket and budget expenditure, patient number, drug policy tool for decision makers			Policy simulator (SAS)
Vincenzo (2000)	Minimal reference price evaluation, effect on drug demand and drug expenditure containment			Econometric model
Yu and Zhao (0214)	Evaluating the impact of drug regulation implementation (ACA) on individuals, health-care providers and pharmaceutical firms; original and generic drug price competition; out-of-pocket payment reduction and increase insurance coverage; drug demand and price			structural model
Leung et al. (2016)	Pharmaceutical product availability, demand and inventory management of essential drugs			DE
Bae et al. (2008)	Co-payment change effect on health outcome and drug expenditure			Markov, state-transition modelling
Spillane et al. (2015)	Evaluation of the effect of the introduction of reference pricing and INN competition, pharmaceutical policy and regulation, generic penetration			Econometric modelling

Literature review: published paper results

Appendix II PhD LitLook.7z

Appendix C

Qualitative modelling

Questions to experts, regarding ERP Resources and Agents Maps and regarding ERP simulation outcomes

Note: Before conducting this interview (first and second stage) with the experts, all presented maps (Resource map, Agent interaction map, Agent behaviour map and Resource Agent map) are explained thoroughly, including all relevant assumptions, and input and output variables connected to the scenario simulator.

Stage I

1. What is your view on the following ERP Resource Map?

    a. Would you believe that the ERP Resource Map contains key pharmaceutical market Resources, their interrelations and influencing factors?

    b. If you believe that any key resources, interrelationships, and or influencing factors are missing, what changes would you suggest?

2. What is your view on the following ERP Agent Interaction Map?

    a. Would you believe that the ERP Agent Interaction Map contains key market Agents, their interrelations and influencing factors?

    b. If you believe that any key market agents, interrelationships, and or influencing factors are missing, what changes would you suggest?

3. What is your view on the following ERP Agent Behaviour Map?

    a. Would you believe that the ERP Agent Behaviour Map contains the main

activity routine of the market Agents, including their condition to action pattern?

b. If you believe that any elements in the main activity routine of the market agents are missing, what changes would you suggest?

4. What is your opinion about the following hybrid ERP Resource Agent Map?

a. Would you believe that the ERP Resource Agent Map contains key market Resources and Agents, their interrelations and influencing factors?

b. If you believe that any key market resources and agents, their interrelations and or influencing factors are missing, what changes would you suggest?

Stage II

1. According to your expert knowledge, what are your expectations about the effects of the following ERP scenario experiments on drug access delays, drug prices evolution and drugs withdrawals:

a. ERP rules parameter variations experiments, including changing price calculation formula (minimum or average price), price revision period (once in 1 or 2 years), reference countries baskets?

b. ERP with or without Parallel trade?

c. ERP with or without drug competition (on patent single drug v off patent market with two or three drug rivals)?

d. ERP with contextual regulation effects (prescribing on drug's brand or on

drug's molecule, mandatory price discounts for drug reimbursement)?

e. ERP vs no ERP scenarios?

2. Would you believe that the ERP scenario simulator can show performance close to your expectations in relation to the above scenario experiments?

4. If you would not, please explain why you think so?

Appendix D

Resource Agent Mapping (RAM pre publishing version)

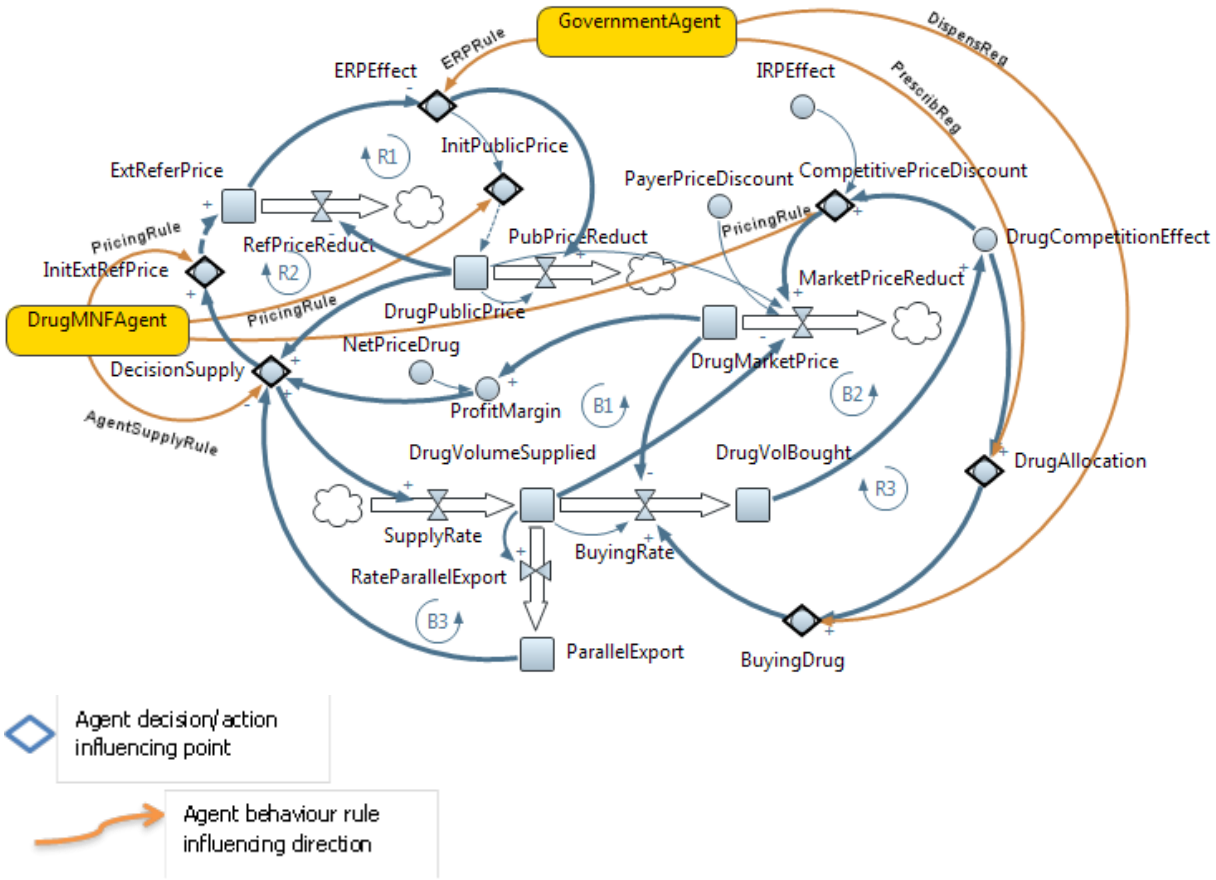


Figure 7.3.2.a (Appendix VII) Hybrid RAM example of a previous version, exhibiting the map area related to two main agents' condition/action behaviour: drug manufacturer and government

Appendix E on simulation validation

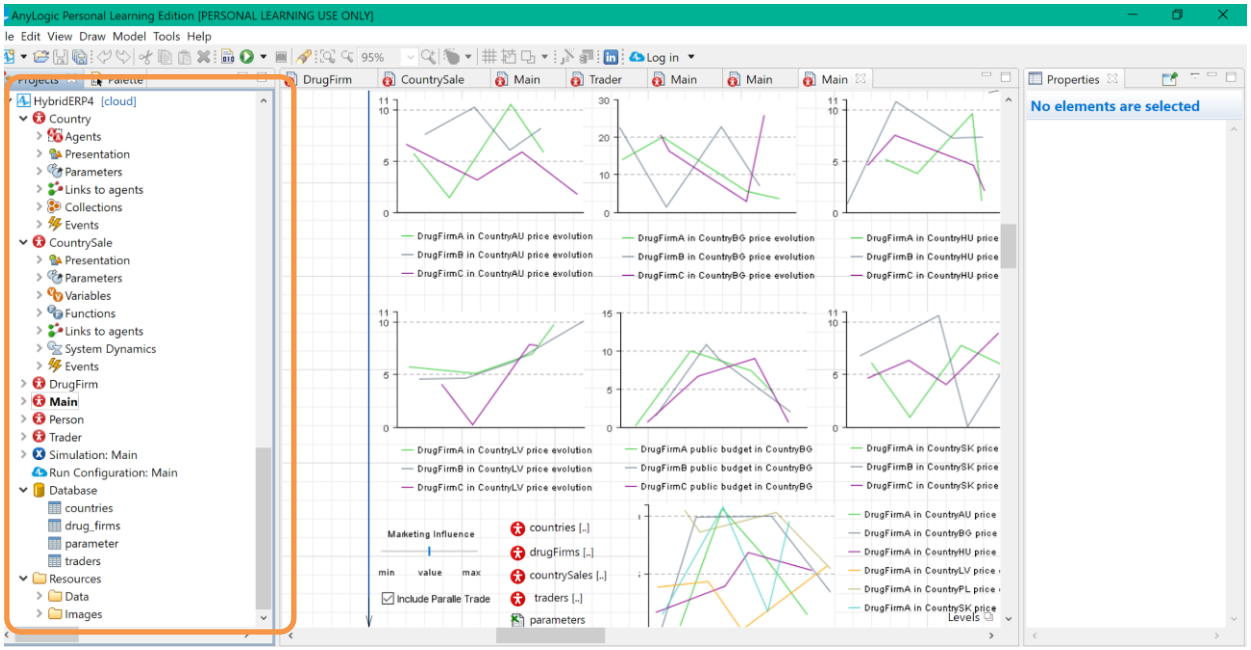


Figure 8.6.5.2 on the simulation design working space of the Anylogic software exhibiting the ERP simulation design structure and functional components

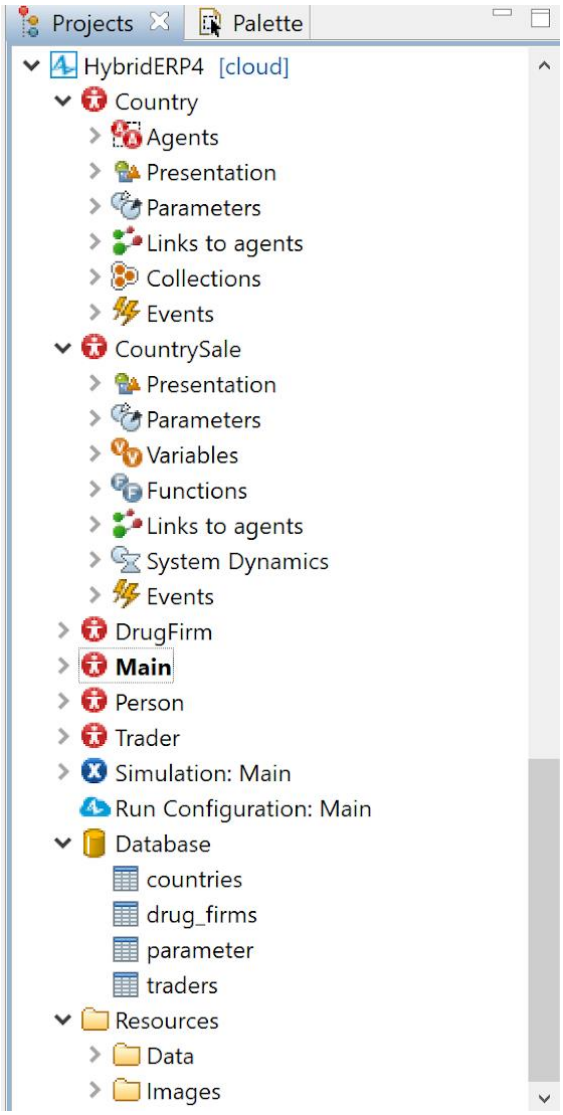


Figure 8.6.5.3 on the 'Projects' view of the Anylogic software where all of the ERP simulation components can be viewed and further inspected through clicking on each of them

Figure 8.6.5.4 Presentation of custom configured simulation control panel (dashboard) including a set of price evolution graphs for selected drugs and reference countries in EU

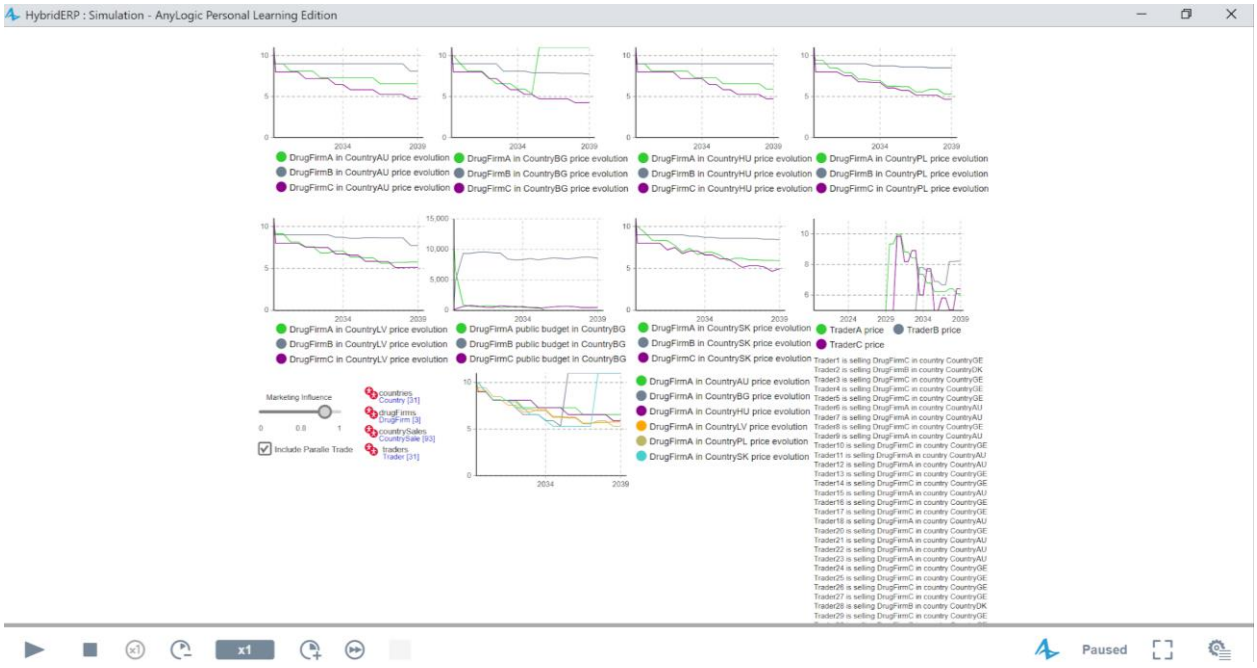


Table 8.6.6.1 Confidence building principles

Authors	Approach to confidence building
Sterman (2000)	Highlights that since a model is a simplified representation of reality it can never be validated and building confidence in a model is more appropriate. Critically assessing model's boundary, time horizon, and level of aggregation in relation to modelling purpose is of key importance and all factors relevant to the modelling purpose need to be captured endogenously in the model boundary.
Heath et al. (2009)	ABM validation with two main stages: conceptual and operational validation, where the built conceptual model needs to correspond to the applied system theory

	and behavioural criteria and the obtained results from the simulation runs need to be consistent to real system behaviour.
Bonabeau (2002)	Accentuated that validation and calibration needed expert judgement
Ormerod and Roswell (2009)	Model replication, model explanation, and outcome explanation and that "behavioural rules should be capable of justification using evidence from outside the model"
Mingers (2000)	Explained model validation from a CR point of view: "… the philosophy is similar to that of CR (as opposed to positivism) in that it is recognized that the main purpose is not accurate prediction of what will occur, but instead greater learning and under-standing of the causal mechanisms involved in the situation. The argument is the same as in CR, namely that social systems are inherently open (although they have to be artificially closed within the modelling process) and that it is impossible to properly quantify the various factors and their relationships.

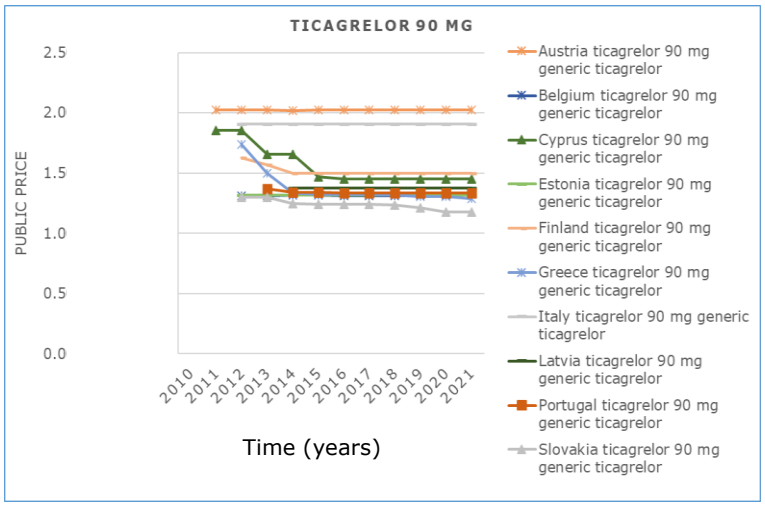


Figure 8.6.6.3 On patent drug Ticagrelor 90 mg price evolution pattern for a 10 year period in selected EU countries (EURIPID data)

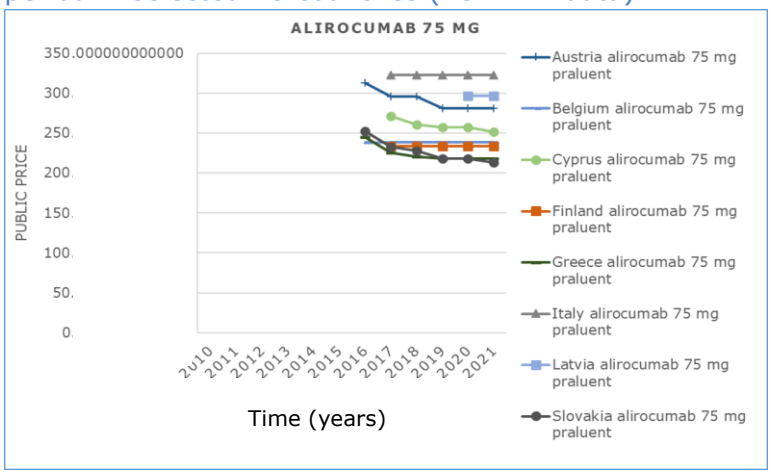


Figure 8.6.6.4 On patent drug Alirocumab 75 mg price evolution pattern for a 10 year period in selected EU countries (EURIPID data)

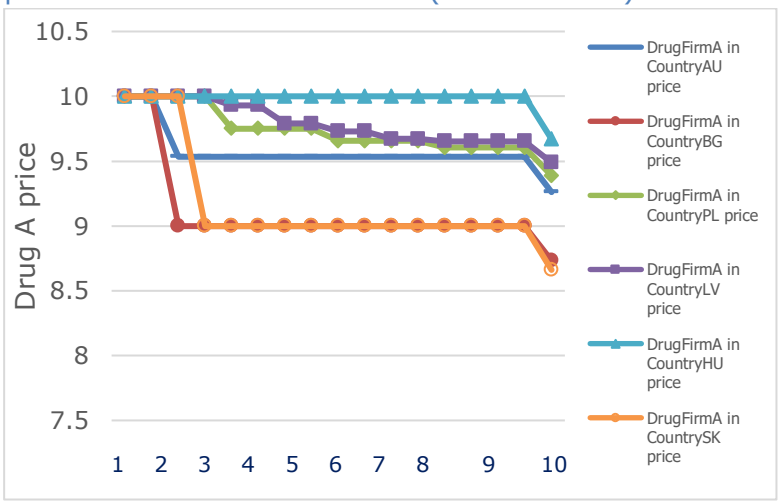


Figure 8.6.6.5 on patent drug A simulated price evolution pattern for a 10 year period in selected six countries (AU, BG, PL, LV, HU, SK)

Figure 8.6.6.10 and Figure 8.6.6.11 provide a comparative "pattern" (Ghaffarzadegan et al. 2011) behaviour of real and simulated drag prices of original and generic clopidogrel 75 mg in selected EU countries like Austria, Bulgaria, Greece, Latvia, Poland, Slovakia.

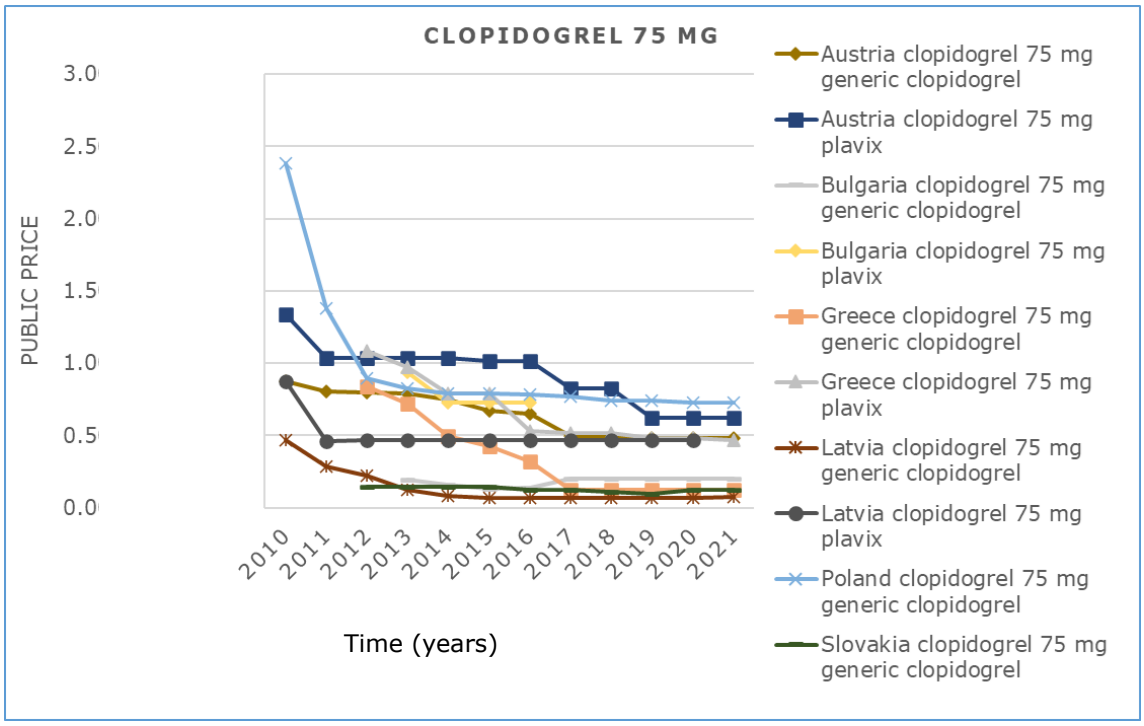


Figure 8.6.6.10 Real drug price evolution pattern for original and generic clopidogrel 75 mg in selected EU countries

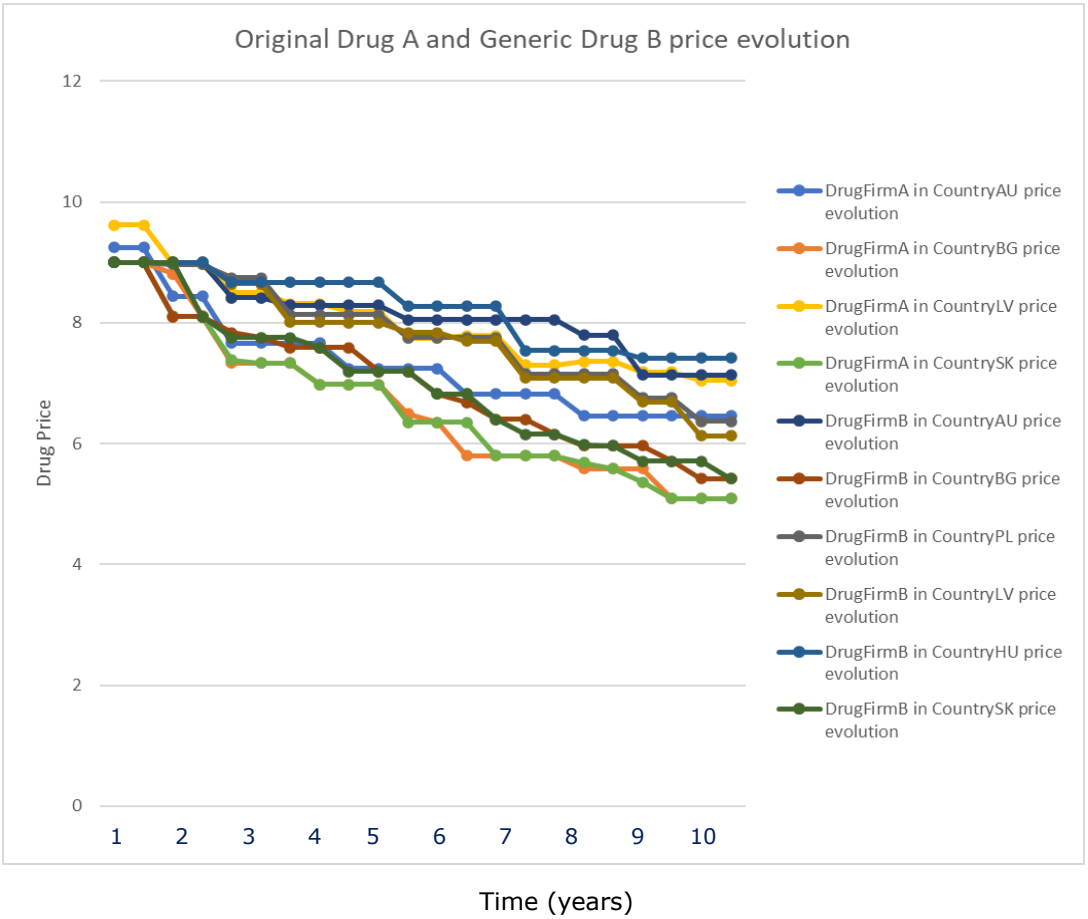
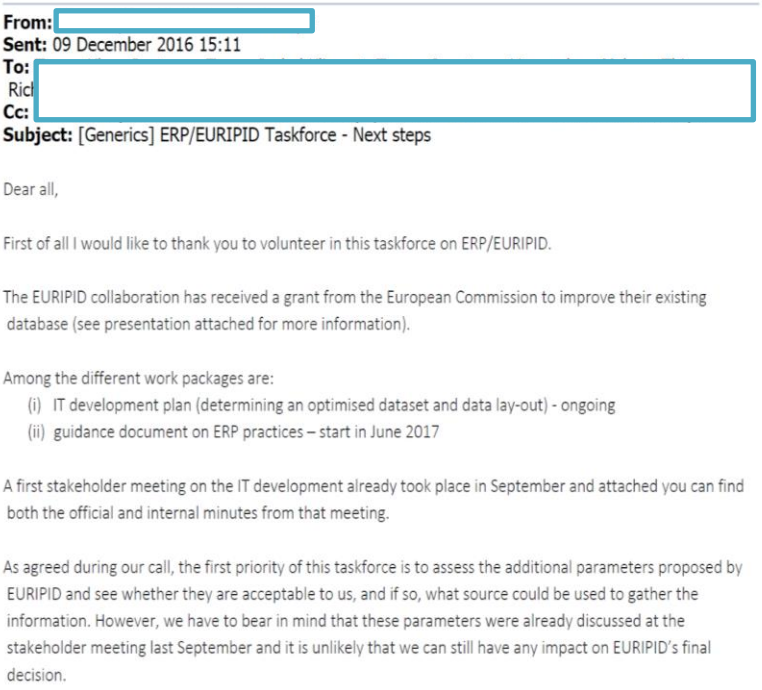


Figure 8.6.6.11 Simulated drug price evolution of drug A (original off patent drug), drug B (generic drug entering market second) and drug C (generic drug coming third), in Austria, Bulgaria, Poland, Latvia, Hungary and Slovakia

Figure 8.6.6.20 EGA task force on ERP and copy of e-mail regarding members (including my name) involvement on the topic



From:
Sent: 09 December 2016 15:11
To:
Rich
Cc:
Subject: [Generics] ERP/EURIPID Taskforce - Next steps

Dear all,

First of all I would like to thank you to volunteer in this taskforce on ERP/EURIPID.

The EURIPID collaboration has received a grant from the European Commission to improve their existing database (see presentation attached for more information).

Among the different work packages are:

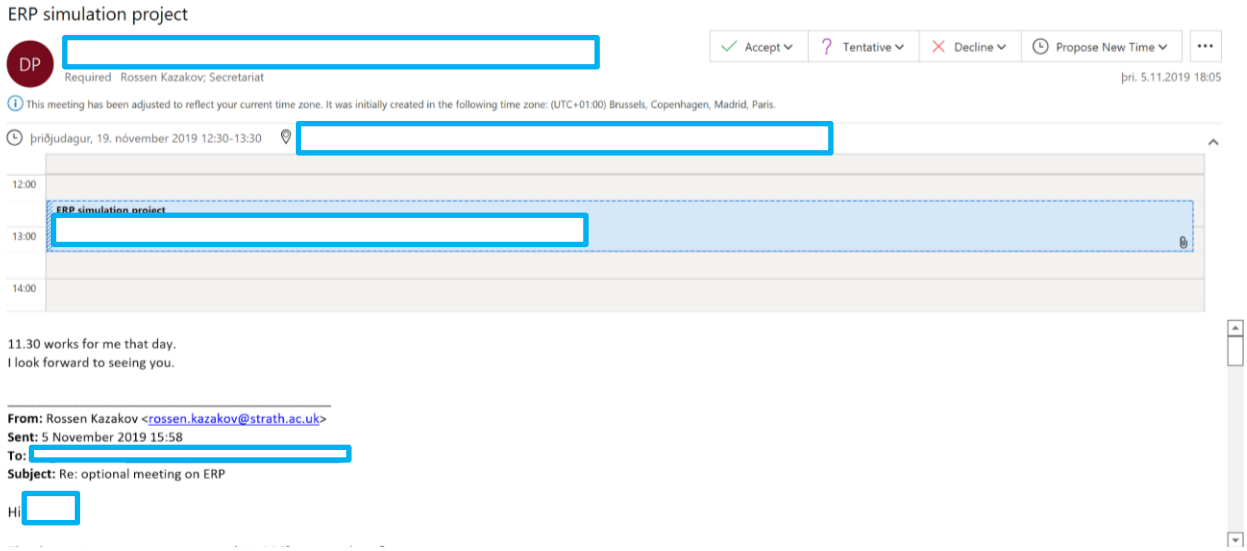
(i) IT development plan (determining an optimised dataset and data lay-out) - ongoing
(ii) guidance document on ERP practices – start in June 2017

A first stakeholder meeting on the IT development already took place in September and attached you can find both the official and internal minutes from that meeting.

As agreed during our call, the first priority of this taskforce is to assess the additional parameters proposed by EURIPID and see whether they are acceptable to us, and if so, what source could be used to gather the information. However, we have to bear in mind that these parameters were already discussed at the stakeholder meeting last September and it is unlikely that we can still have any impact on EURIPID's final decision.

Figure 8.6.6.21 and Figure 8.6.6.22 provide examples of an email for scheduling a meeting with Medicines Industry Association in Brussels and a document containing meeting notes with subject experts.

Figure 8.6.6.21 E-mail for scheduling one of the meetings with Medicines for Europe in their Brussels offices


ERP simulation project

DP

Required Rossen Kazakov; Secretariat

Accept Tentative Decline Propose New Time

þri. 5.11.2019 18:05

This meeting has been adjusted to reflect your current time zone. It was initially created in the following time zone: (UTC+01:00) Brussels, Copenhagen, Madrid, Paris.

þriðjudagur, 19. nóvember 2019 12:30-13:30

12:00

ERP simulation project

13:00

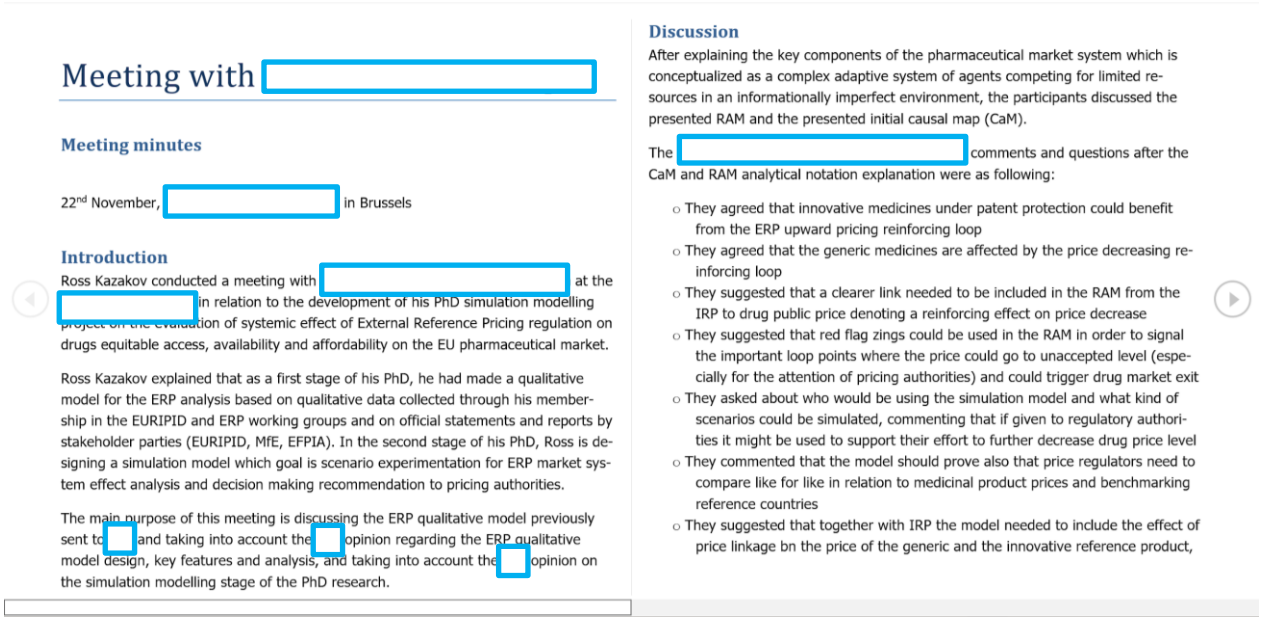
14:00

11.30 works for me that day.
I look forward to seeing you.

From: Rossen Kazakov <rossen.kazakov@strath.ac.uk>
Sent: 5 November 2019 15:58
To:
Subject: Re: optional meeting on ERP

Hi

Figure 8.6.6.22 Copy of meeting notes minutes transferred in word document (meeting with Medicines Industry Association)


Meeting with

Meeting minutes

22nd November, in Brussels

Introduction

Ross Kazakov conducted a meeting with at the in relation to the development of his PhD simulation modelling project on the evaluation of systemic effect of External Reference Pricing regulation on drugs equitable access, availability and affordability on the EU pharmaceutical market.

Ross Kazakov explained that as a first stage of his PhD, he had made a qualitative model for the ERP analysis based on qualitative data collected through his membership in the EURIPID and ERP working groups and on official statements and reports by stakeholder parties (EURIPID, MfE, EFPIA). In the second stage of his PhD, Ross is designing a simulation model which goal is scenario experimentation for ERP market system effect analysis and decision making recommendation to pricing authorities.

The main purpose of this meeting is discussing the ERP qualitative model previously sent to and taking into account the opinion regarding the ERP qualitative model design, key features and analysis, and taking into account the opinion on the simulation modelling stage of the PhD research.

Discussion

After explaining the key components of the pharmaceutical market system which is conceptualized as a complex adaptive system of agents competing for limited resources in an informationally imperfect environment, the participants discussed the presented RAM and the presented initial causal map (CaM).

The comments and questions after the CaM and RAM analytical notation explanation were as following:

- They agreed that innovative medicines under patent protection could benefit from the ERP upward pricing reinforcing loop
- They agreed that the generic medicines are affected by the price decreasing reinforcing loop
- They suggested that a clearer link needed to be included in the RAM from the IRP to drug public price denoting a reinforcing effect on price decrease
- They suggested that red flag zings could be used in the RAM in order to signal the important loop points where the price could go to unaccepted level (especially for the attention of pricing authorities) and could trigger drug market exit
- They asked about who would be using the simulation model and what kind of scenarios could be simulated, commenting that if given to regulatory authorities it might be used to support their effort to further decrease drug price level
- They commented that the model should prove also that price regulators need to compare like for like in relation to medicinal product prices and benchmarking reference countries
- They suggested that together with IRP the model needed to include the effect of price linkage bn the price of the generic and the innovative reference product,

Table 8.6.6.9 Main quotes showing ERP experts opinion

Expert	Opinion quotes (from researchers notes)
1. [redacted] Medicines Industry Association	What prices are made public? Make account for variation in countries ERP baskets Currencies fluctuation rates? Price linkages IRP (internal reference pricing) price alignment? API prices and availabilities? Introduce higher competition through more generic drug companies Control over volume rates? Who will be using this ERP simulation
2. Independent pharmaceutical expert	'Interesting research into the impact and function of external reference pricing' ERP simulation scenarios have close to real market drug price behaviour It allows for experiments with different degrees of market competition, including INN (MOLECULE NAME), therapeutic group or brand competition Parallel trade effects are also made possible for exploration which brings out important insights

3. Independent expert and former senior manager in international innovative and generic companies	ERP effects could be explored in the simulation experiments also through introducing ERP and prescribing regulation changes during the simulation run It is important to have the possibilities to explore interfering effects of competition and parallel trade on the ERP and prices
4. Representative of Medicines Company	Innovative products could be delayed or unavailable due to ERP rules and interfering state public made discounts
5. Representative member of pharmaceutical pricing association	On the presented ERP simulation, the innovative on patent drugs prices do not decline ERP simulation does not take into account state imposed discounts like in our DE simulation, where the innovative drug enters first Austrian market and then enters with discount in Italian market ERP in Austria is applied for innovative drugs while price linkage transfers it to generic drugs
6. Anonymous representative of pricing authorities	Simulation outcome results are correct in taking account of ERP effects among reference basket countries, local prescribing regulation, but PT effects are logical but hard to make account of in the market Drug market exits do not make problem if there are remaining generic drug rivals

7. Representative of local Medicines Industry Association	ERP simulation scenarios represent a correct view of the market competition and prescribing regulation and their interference with ERP rules and drug prices Parallel trade can have also effect on generic drugs Price calculation formula and ERP countries basket are very important features, like also price revision period, which can influence quicker or slower price decrease
8. Anonymous pricing authorities expert	Price behaviour of innovative and generic drug are logical and correct Price discounts requirement could have effect on market launch and price regulators need to be careful and good negotiators
9. Anonymous pricing authorities expert	Other requirements like drug market presence in other reference countries prior to local market entry can have effect on drug delay Important question is connected to capturing market competition price discounts in order to make ERP regulation effective

Table 8.6.6.2.a Ticagrelor real vs. simulated data in a table format

	Ticagrelor in BG	DrugFirmA in CountryAU price evolution	DrugFirmA in CountryBG price evolution	DrugFirmA in CountryPL price evolution	DrugFirmA in CountryLV price evolution	DrugFirmA in CountryHU price evolution	DrugFirmA in CountrySK price evolution
1	112.26	100	114	100.00	100.00	100.00	100.00
2	109.19	100	102.60	100	100	100	100
3	109	90.847	102.60	100.00	100.00	100.00	90
4	108.84	90.847	102.60	90.78	90.95	100.00	90
5	108.51	90.847	102.60	90.78	90.81	100.00	90
6	107.67	90.847	102.60	90.68	90.76	100.00	90
7	106.18	90.847	102.60	90.68	90.69	100.00	90
8	105.89	90.847	102.60	90.68	90.67	100.00	90
9	89.75	90.847	92.08	90.68	90.67	100.00	90
10		90.556		90.42	90.52	90.92	80.908

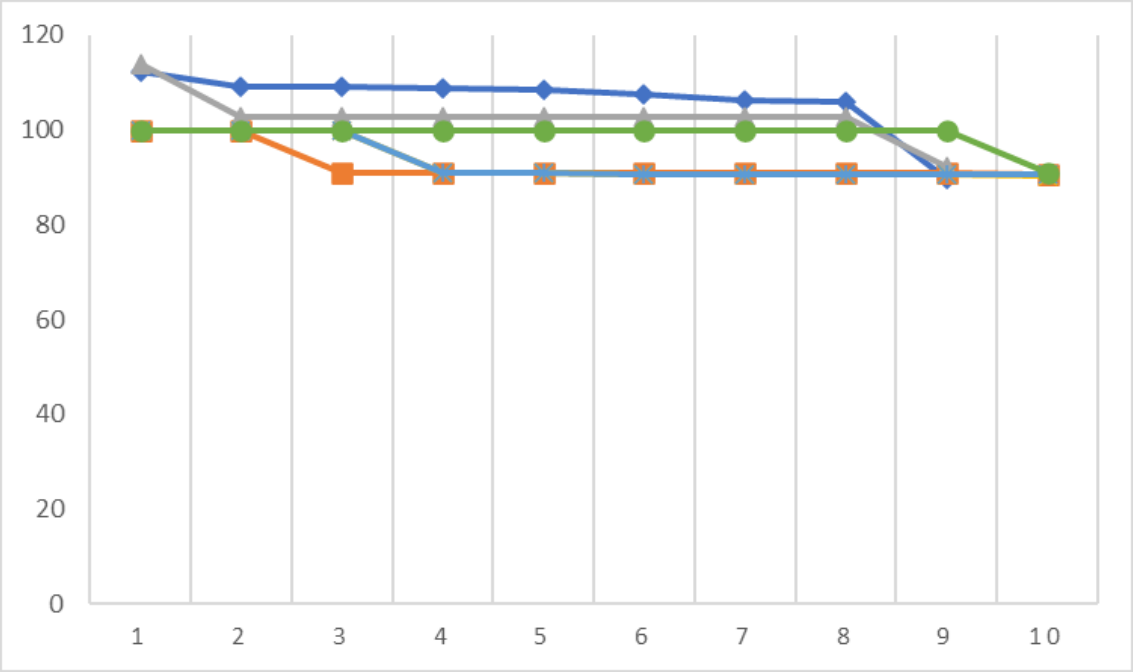


Table 8.6.6.2.b Original and generic Clopidogrel in Bulgaria

	Plavix	KALDERA generic	Trombex			
	Original		Generic	Drug A	Drug B	Drug C
2009	70.76			70		
2010	70.76	31.29	29.45	70	32	30
2011	70.76	31.29	29.45	49	32	30
2012	70.76	22.06	29.45	34.3	22.4	21
2013	70.76	12.38	29.45	24.01	15.68	14.7
2014	17.6	5.12	12.71	24.01	15.213	13.912
2015	13.69	5.12	5.32	16.807	15.213	9.739
2016		5.12	5.01		10.649	6.817
2017		5.12	5.01		10.649	6.817
2018		5.12	5.01		7.455	6.817
2019		5.12	5.01		7.455	
2020		5.12	5.01		5.218	

Table 8.6.6.2.c Original and generic Clopidogrel in Austria

ACTIVE SUBSTANCE/ BRAND	min_GROSS_2010	min_GROSS_2011	min_GROSS_2012	min_GROSS_2013	min_GROSS_2014	min_GROSS_2015	min_GROSS_2016	min_GROSS_2017	min_GROSS_2018	min_GROSS_2019	min_GROSS_2020	min_GROSS_2021
generic clopidogrel	0.875	0.803333	0.798333	0.791667	0.75	0.671667	0.65	0.493333	0.491667	0.483333	0.483333	0.483333
Original brand plavix	1.339286	1.039286	1.039286	1.039286	1.035714	1.017857	1.017857	0.828571	0.828571	0.621429	0.621429	0.621429

Table 8.6.6.2.d Original and generic Atorvastatin in Bulgaria

	Lipitor	Torvacard	Aragil			
	Original	Generic	Generic	Drug A	Drug B	Drug C
2009	25.62			26		
2010	25.62			26		
2011	25.62	5.79	6.45	26	6	5
2012	17.84	5.79	4.79	18.2	6	5
2013	17.84	4.36	4.79	12.74	6	4.5
2014	12.77	3.15	4.79	12.74	5.4	4.05
2015	7.53	2.39	3.13	6.243	4.86	4.05
2016	7.53	2.39	3.13	4.37	4.374	3.28
2017	7.53	2.39	3.13	3.059	3.937	3.28
2018	7.53	2.39	3.13	3.059	3.543	2.657
2019	2.49	2.39	3.13	3.059	3.543	2.657
2020	2.49	2.39	3.13	2.141	3.543	2.657

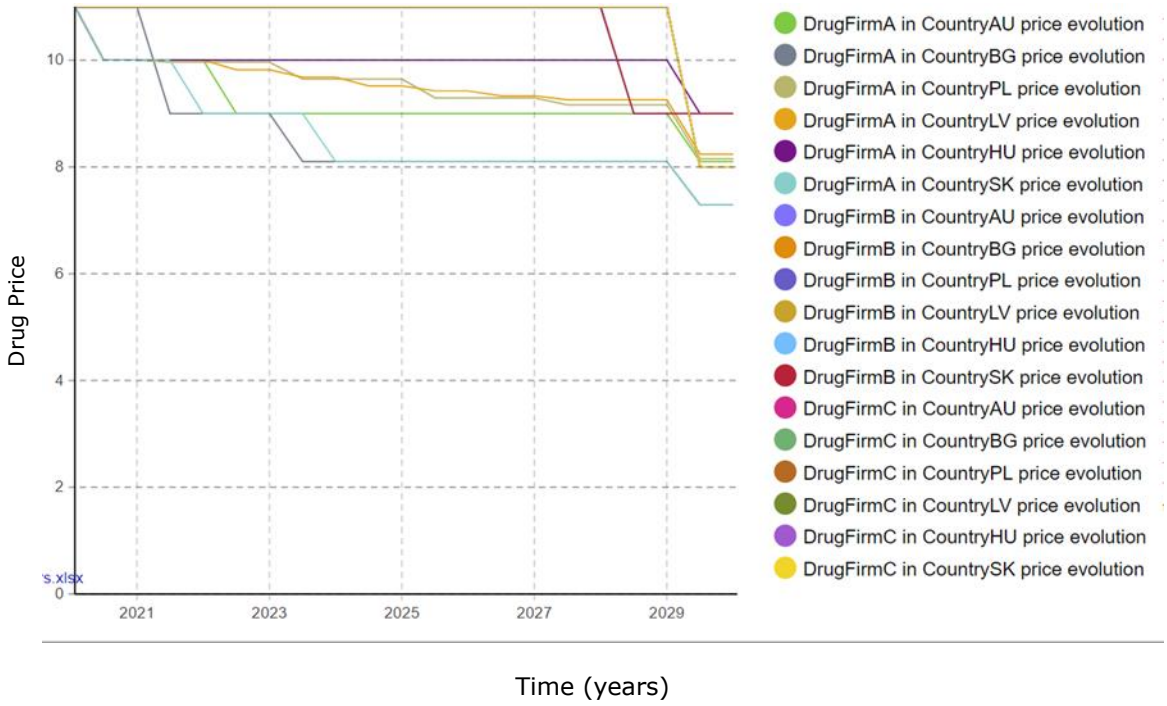


Figure 8.6.6.5.b On patent drug A simulated price evolution pattern for a 10 year period in selected six countries (AU, BG, PL, LV, HU, SK)

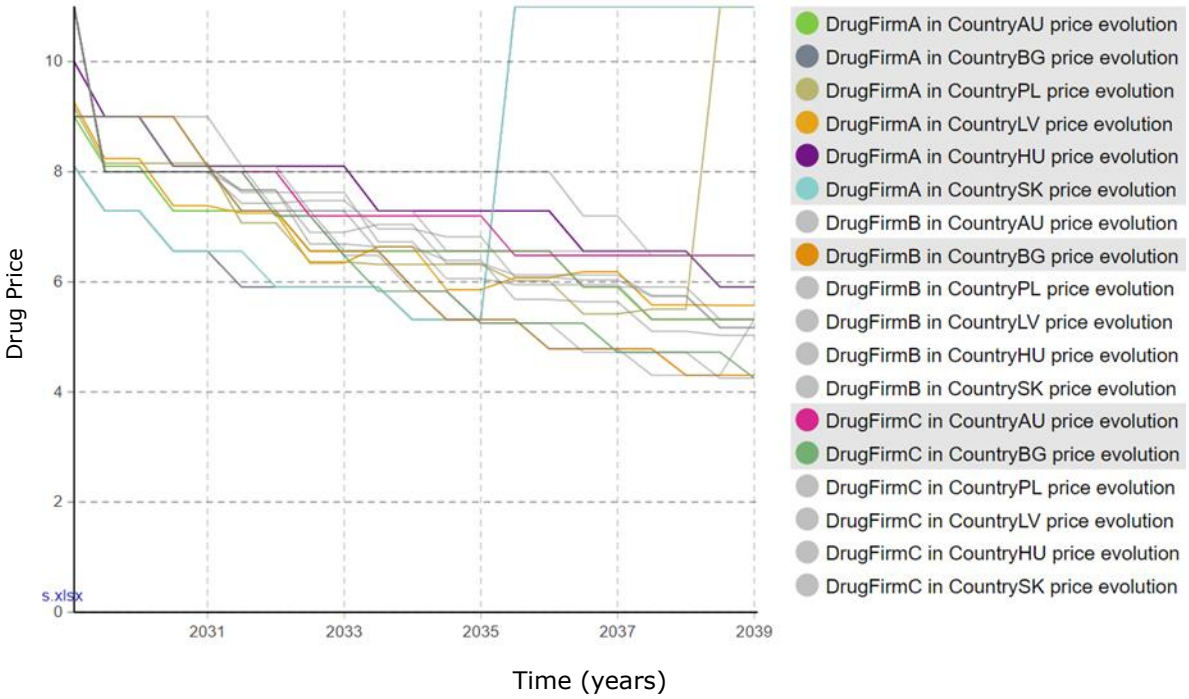


Figure 8.6.6.11.b Simulated drug price evolution of drug A (original off patent drug), drug B (generic drug entering market second) and drug C (generic drug coming third), in Austria, Bulgaria, Poland, Latvia, Hungary and Slovakia

Microsoft Excel
97-2003 Worksheet

Table 8.6.6.A Trend analysis for public drug price evolution in EU selected countries and selected medicines innovative and generic drugs

COUNTRY	STRENGTH	ACTIVE SUBSTANC	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Austria	atorvastatin 10 mg	generic atorvastatin			0.44	0.40	0.37	0.36	0.36	0.31	0.31	0.28	0.27	0.26
Austria	atorvastatin 10 mg	sortis	1.40	1.40	0.58	0.46	0.46	0.46	0.46	0.46	0.46	0.40	0.40	0.40
Austria	clopidogrel 75 mg	generic clopidogrel	0.88	0.80	0.80	0.79	0.75	0.67	0.65	0.49	0.49	0.48	0.48	0.48
Austria	clopidogrel 75 mg	plavix	1.34	1.04	1.04	1.04	1.04	1.02	1.02	0.83	0.83	0.62	0.62	0.62
Bulgaria	atorvastatin 10 mg	generic atorvastatin				0.10	0.08	0.08	0.08	0.08	0.08	0.07	0.07	0.07
Bulgaria	atorvastatin 10 mg	sortis				0.88	0.63	0.38	0.38	0.38	0.38			
Bulgaria	clopidogrel 75 mg	generic clopidogrel				0.20	0.16	0.13	0.14	0.20	0.20	0.20	0.20	0.20
Bulgaria	clopidogrel 75 mg	plavix				0.94	0.73	0.73	0.73					
Latvia	atorvastatin 10 mg	generic atorvastatin	0.15	0.11	0.12	0.07	0.05	0.04	0.04	0.04	0.04	0.04	0.04	0.04
Latvia	atorvastatin 10 mg	sortis	0.43	0.31	0.40	0.39	0.39	0.39	0.39	0.39	0.26	0.26	0.26	
Latvia	clopidogrel 75 mg	generic clopidogrel	0.47	0.29	0.22	0.13	0.09	0.07	0.07	0.07	0.07	0.07	0.07	0.07
Latvia	clopidogrel 75 mg	plavix	0.88	0.46	0.47	0.47	0.47	0.47	0.47	0.47	0.47	0.47	0.47	
Poland	atorvastatin 10 mg	generic atorvastatin	0.43	0.34	0.27	0.22	0.17	0.17	0.15	0.15	0.15	0.15	0.15	0.15
Poland	clopidogrel 75 mg	generic clopidogrel	2.38	1.38	0.90	0.82	0.79	0.79	0.79	0.77	0.74	0.74	0.73	0.73
Poland	clopidogrel 75 mg	plavix	3.76	2.98										
Poland	valsartan 160 mg	generic valsartan	1.41	1.29	0.88	0.86	0.83	0.82	0.79	0.74	0.72	0.72	0.63	0.60
Slovakia	atorvastatin 10 mg	generic atorvastatin			0.04	0.04	0.04	0.06	0.06	0.06	0.06	0.05	0.06	0.06
Slovakia	atorvastatin 10 mg	sortis			0.57	0.39	0.25	0.25						
Slovakia	clopidogrel 75 mg	generic clopidogrel			0.15	0.15	0.15	0.15	0.12	0.12	0.11	0.09	0.12	0.12

A number of drug price evolution graphs per ERP countries, with calculated "trend lines" (MS Excel) are selected to support drug price evolution "pattern" analysis. Real drug price data are taken from the Euripid data base.

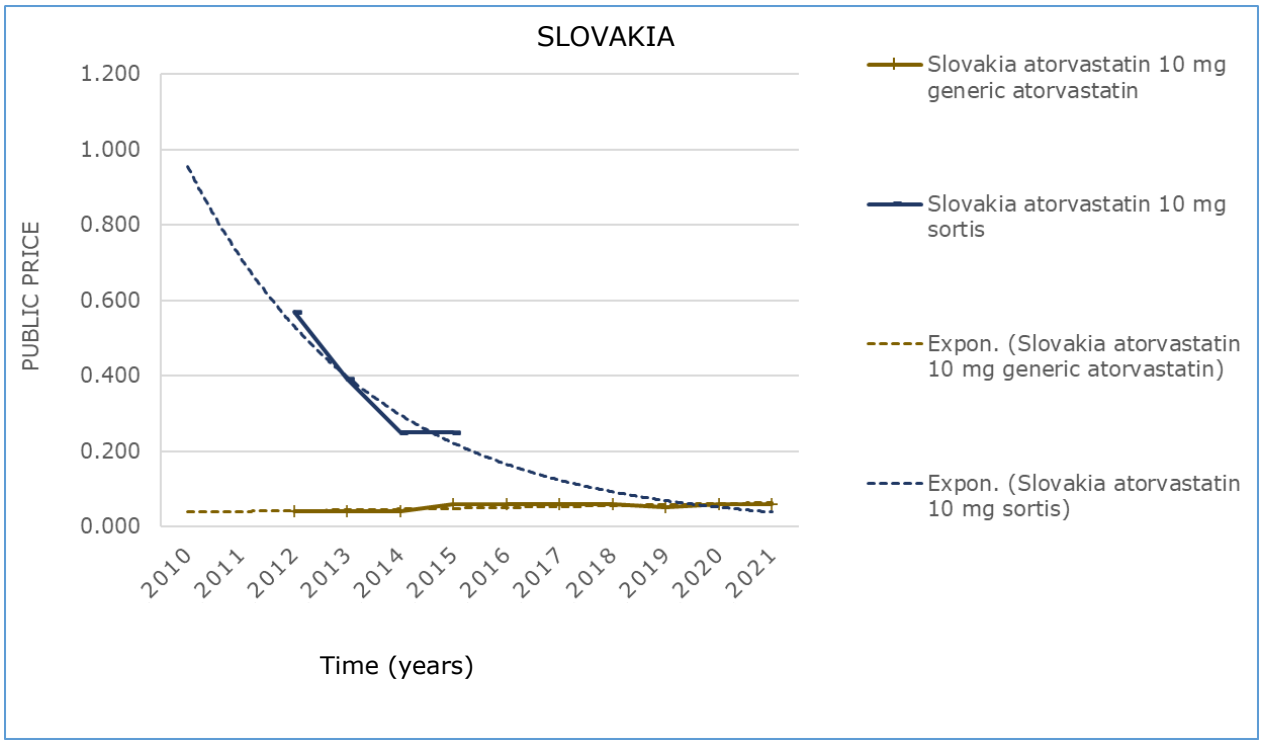


Figure 8.6.6.12 Drug public price real data with trend lines for original brand and generic atorvastatin 10 mg in Slovakia (Source: EURIPID)

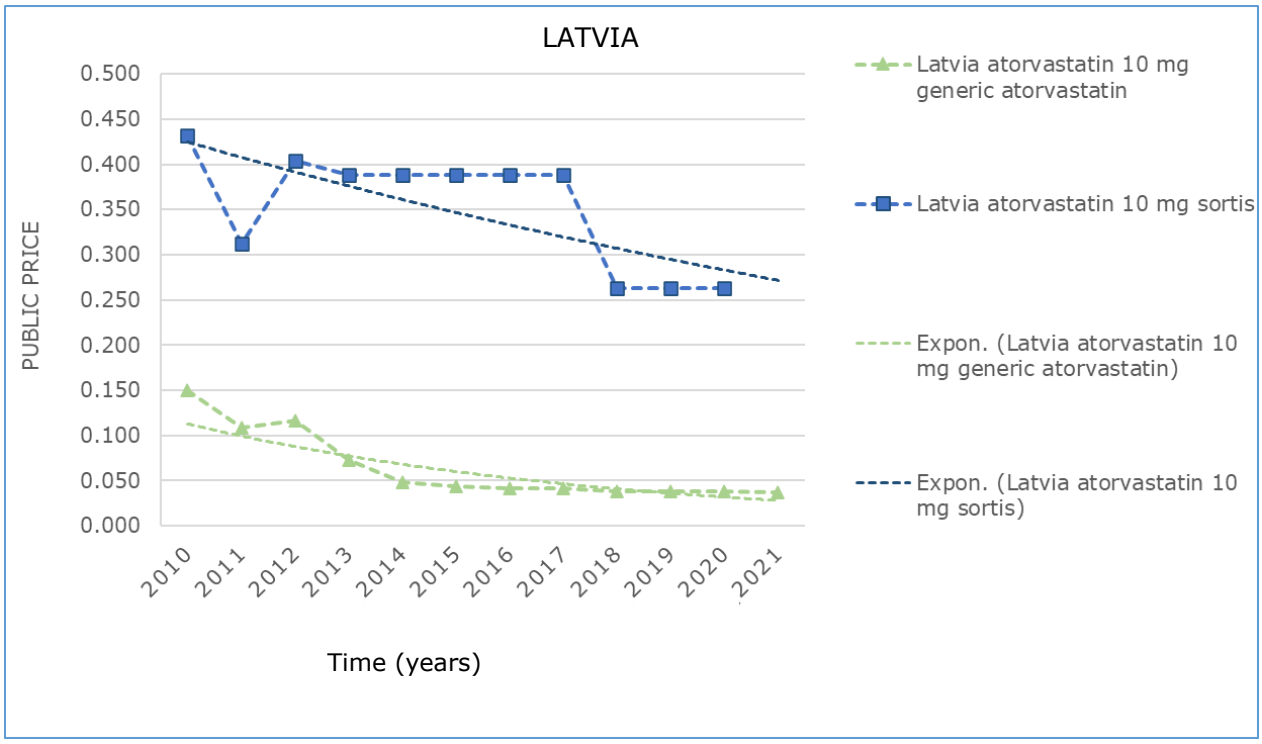


Figure 8.6.6.13 Drug price real data with trend lines for original brand and generic atorvastatin 10 mg in Latvia (Source: EURIPID)

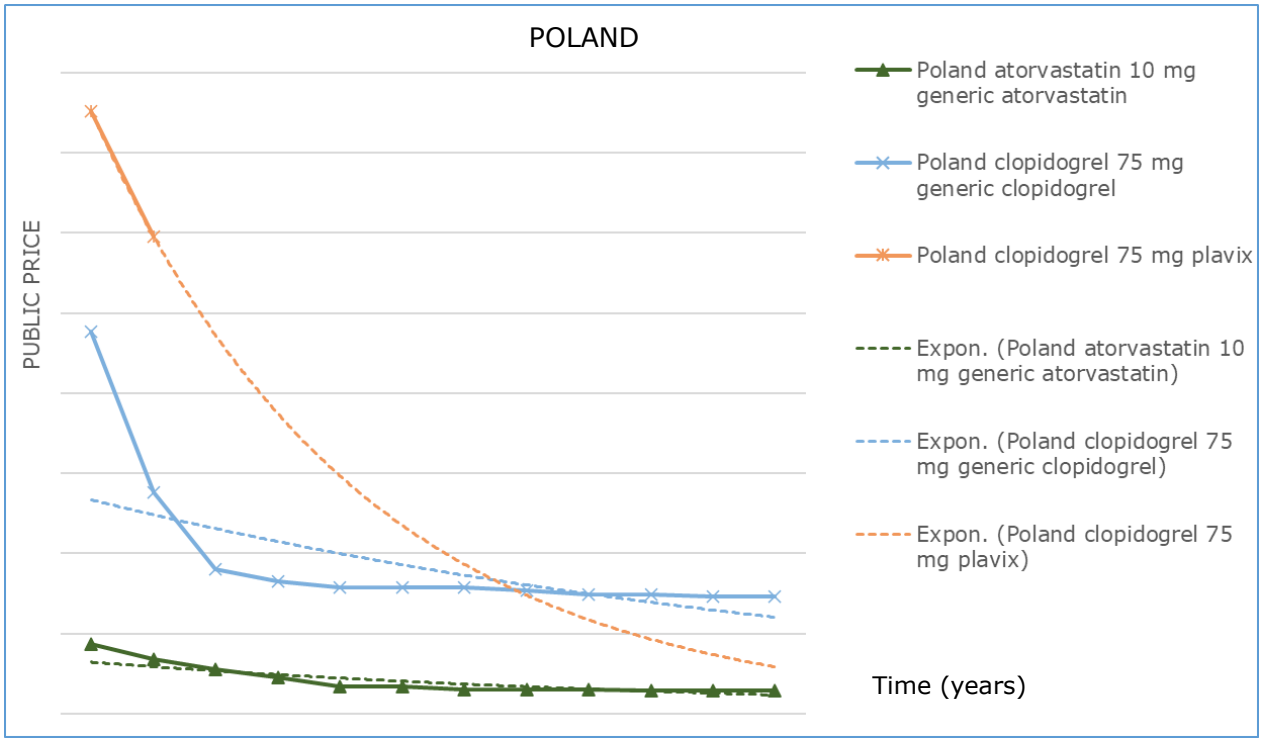


Figure 8.6.1.14 Drug Public price real data for atorvastatin 10 mg and clopidogrel 75 mg original and generic brands in Poland (Source: EURIPID)

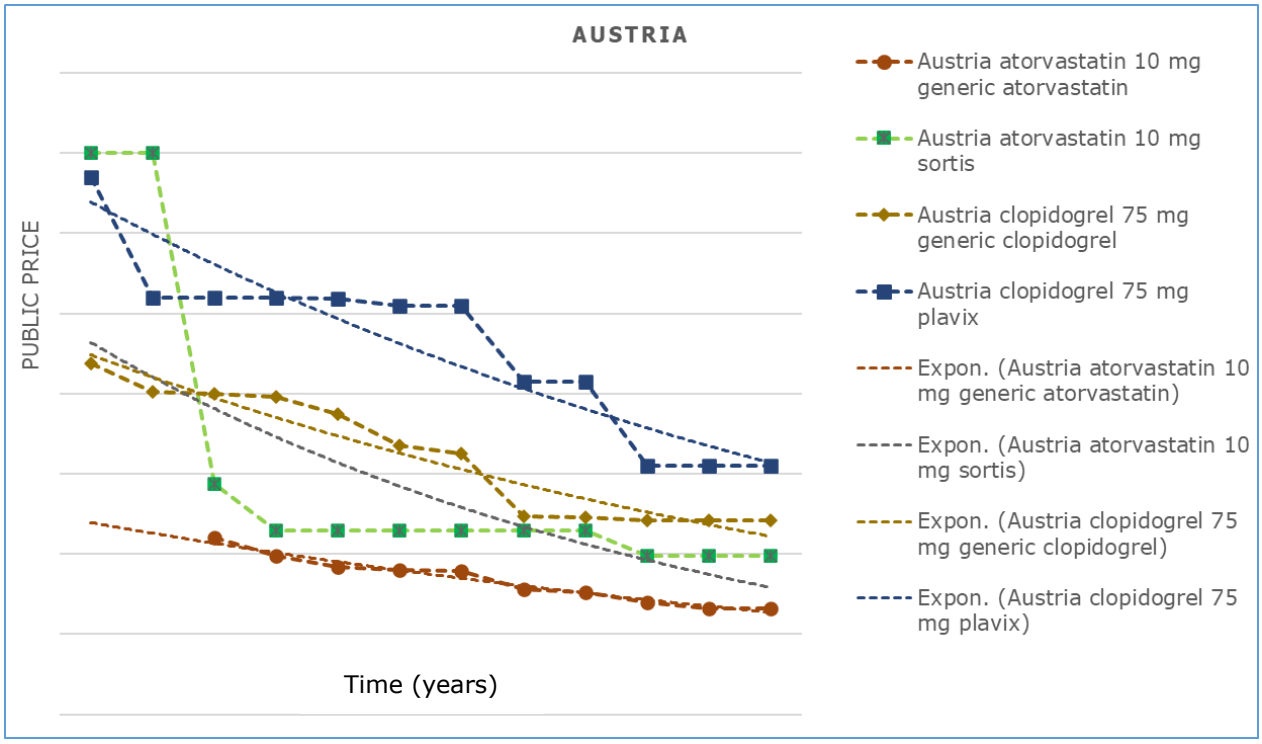


Figure 8.6.6.15 Drug public price real data pr atorvastatin 10 mg and clopidogrel 75 mg original and generic brands in Austria (source: EURIPID)

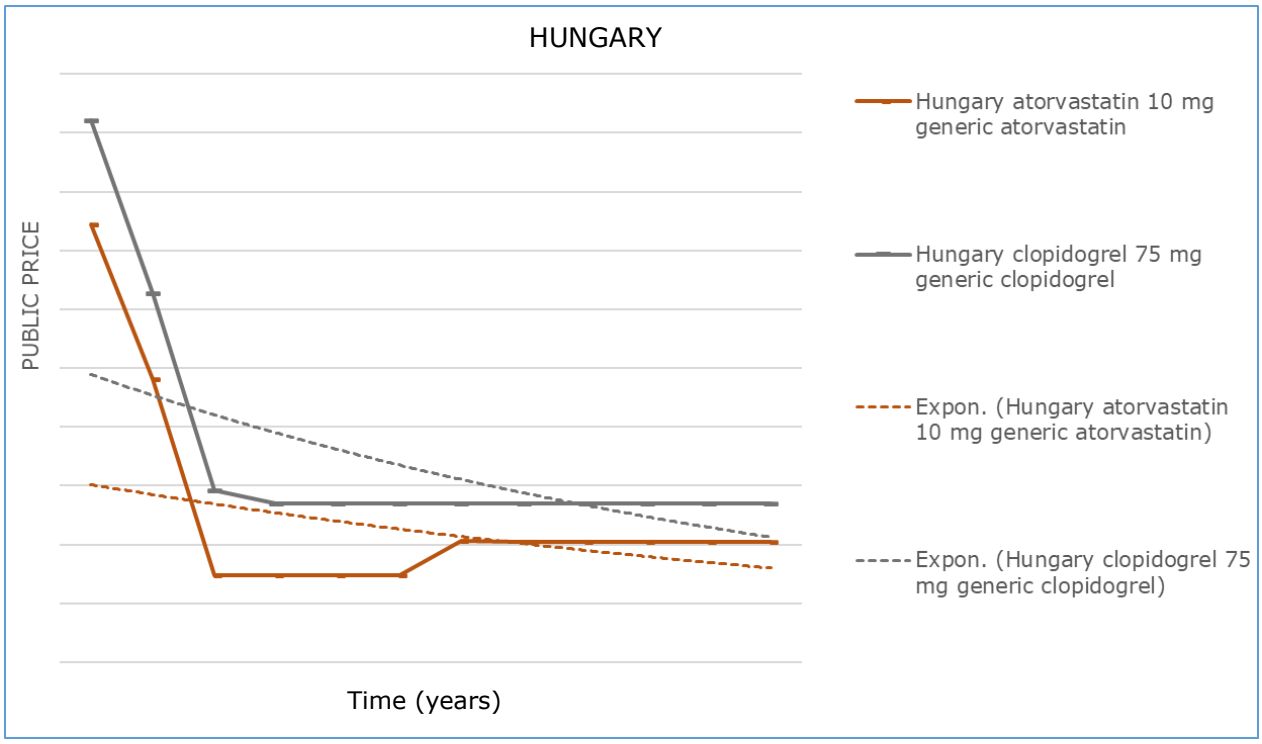


Figure 8.6.6.16 Drug public price real data for atorvastatin 10 mg and clopidogrel 75 mg generic brands in Hungary (source: EURIPID)

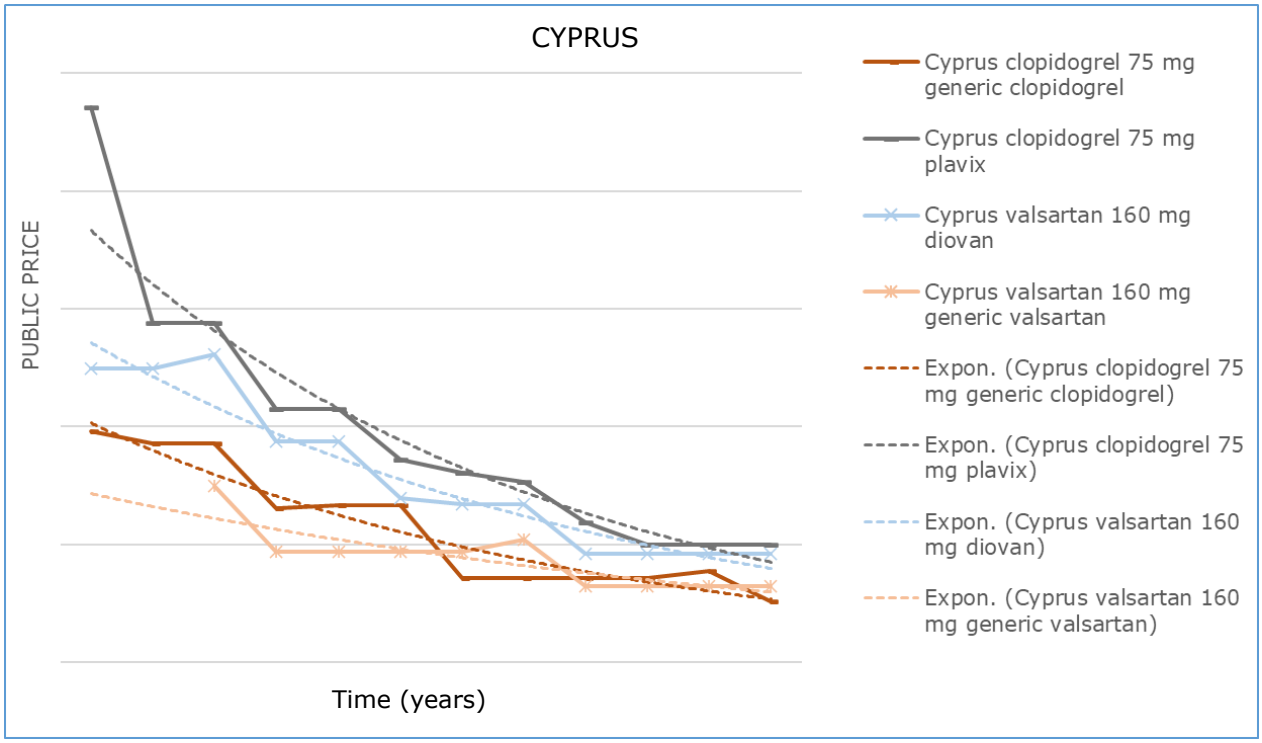


Figure 8.6.6.17 Drug public price real data for Cyprus, original and generic brands clopidogrel 75 mg and Valsartan 160 mg (Source: EURIPID)

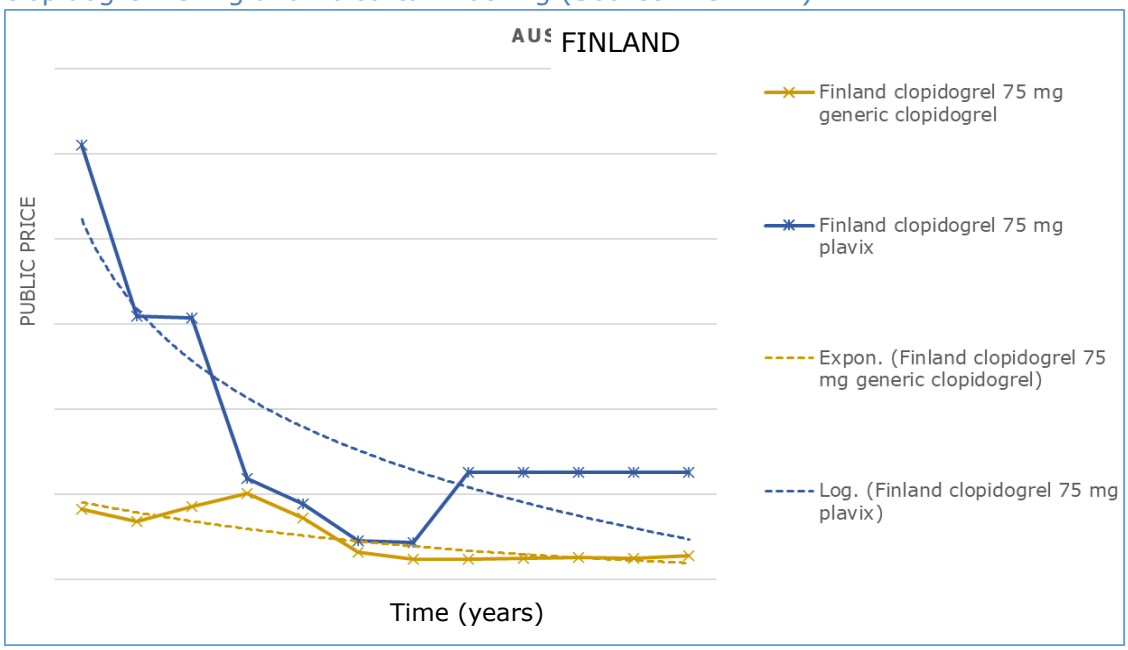


Figure 8.6.6.18 Drug public price real data for clopidogrel 75 mg original and generic brands in Finland (Source: EURIPID)

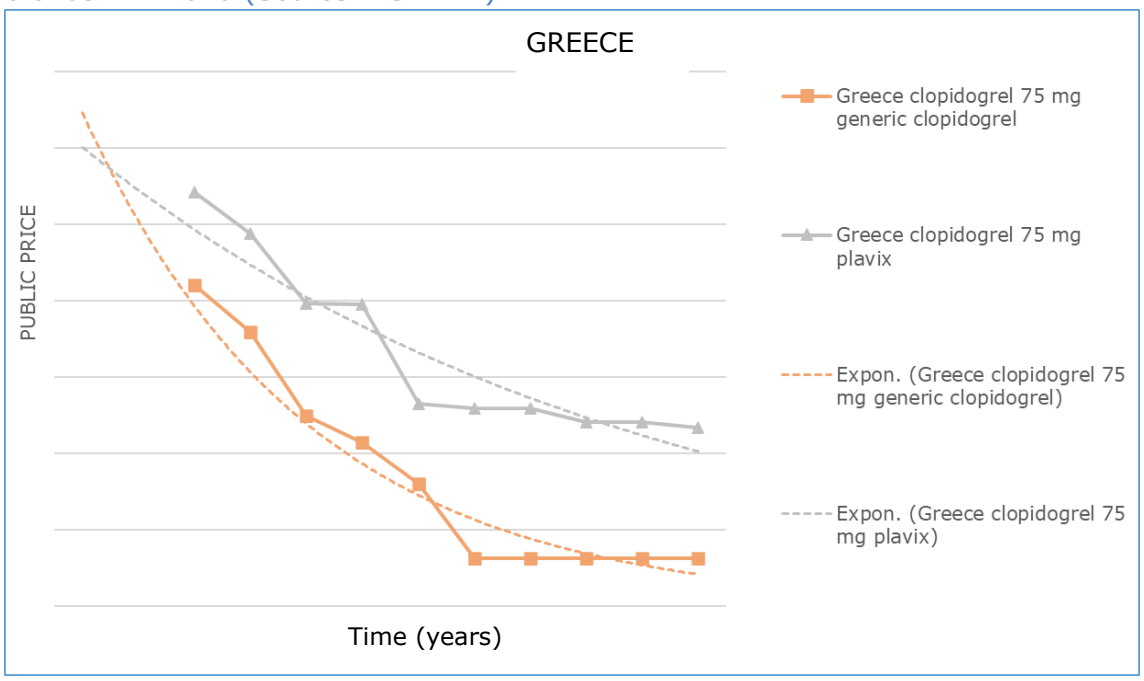


Figure 8.6.6.19 Drug public price real data for clopidogrel 75 mg original and generic brands in Greece

Appendix F

Figure A and B Appendix A ERP with Parallel Trade vs ERP, No Parallel Trade for all EU countries

Figure B Appendix A ERP with Parallel Trade

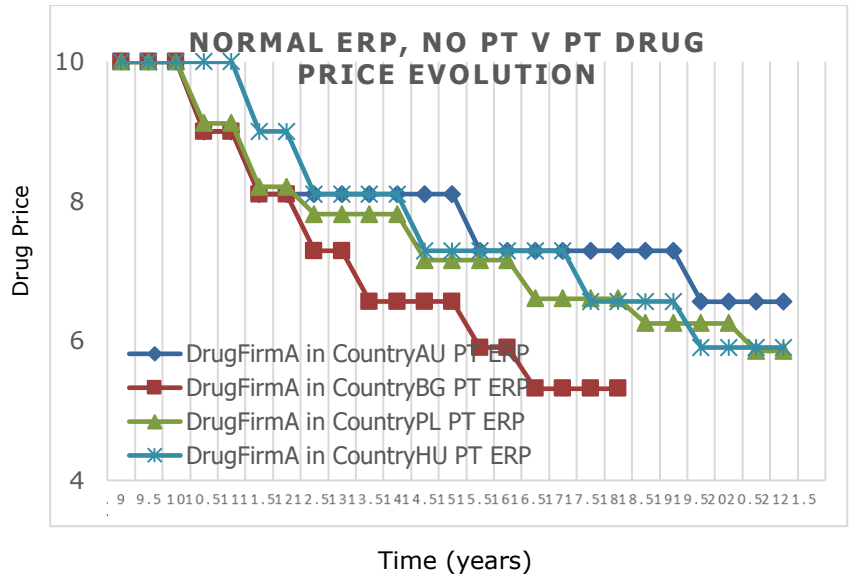


Figure 9.2.1.4 Appendix A Drug A price evolution across four EU markets selected for comparative reasons (Austria, Bulgaria, Poland, Hungary)

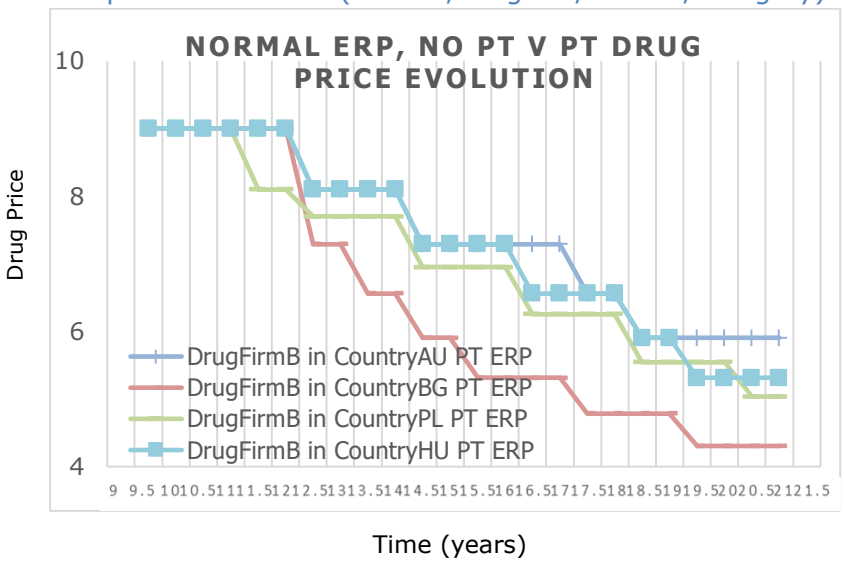


Figure 9.2.1.5 Appendix A Drug B price evolution in the same four EU countries

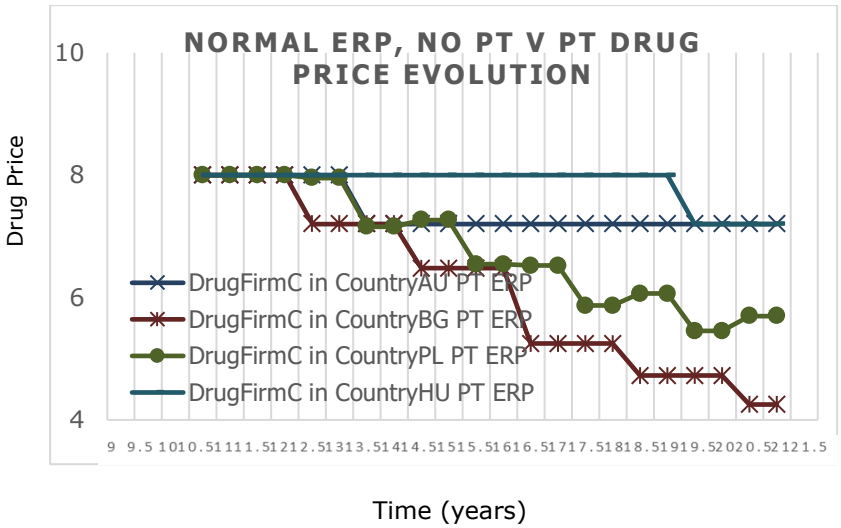


Figure 9.2.1.6. Appendix A Drug C price evolution in the same EU markets

Figure 9.3.1 a. Appendix A Anylogic software output panel for 'no ERP, no parallel trade', price evolution for drug A, B, C in Austria, Bulgaria, Poland, Hungary, Latvia and Slovakia

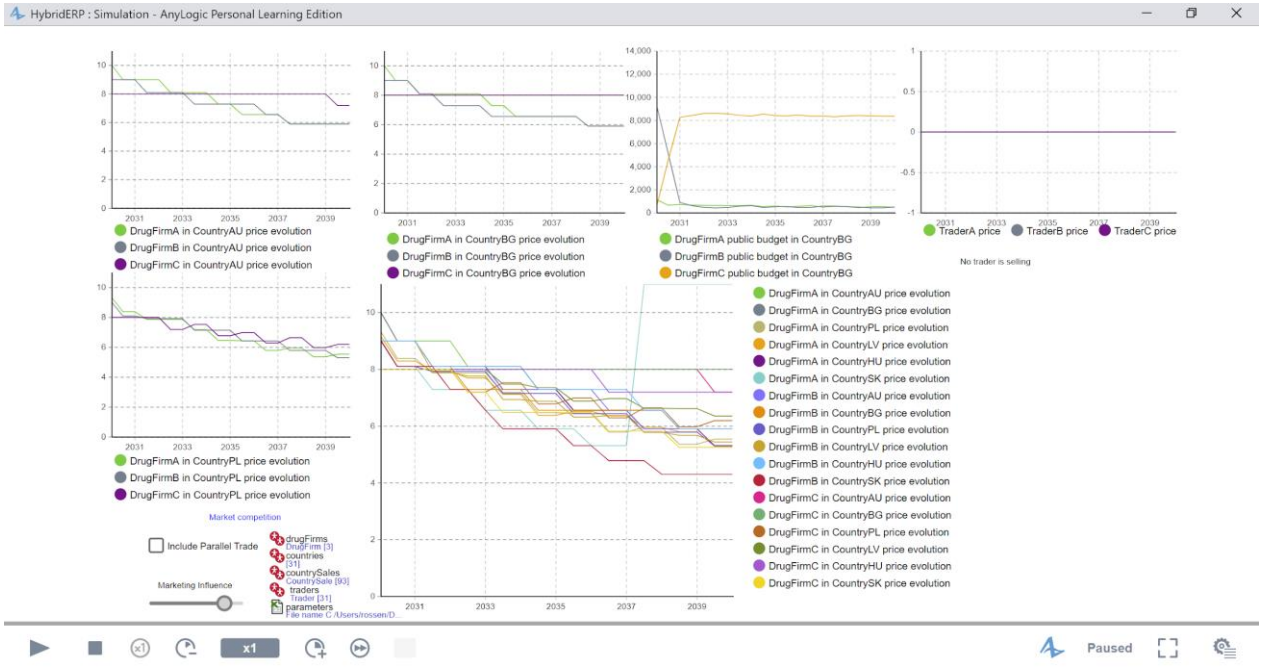


Figure 9.3.1 b. Appendix A Anylogic software output panel for 'no ERP, with parallel trade', price evolution for drug A, B, C in same countries

	DrugFirmA in CountryAU ERP	DrugFirmA in CountryBG ERP	DrugFirmA in CountryPL ERP	DrugFirmA in CountryLV ERP	DrugFirmA in CountryHU ERP	DrugFirmA in CountrySK ERP	DrugFirmB in CountryAU ERP	DrugFirmB in CountryBG ERP	DrugFirmB in CountryPL ERP	DrugFirmB in CountryLV ERP	DrugFirmB in CountryHU ERP	DrugFirmB in CountrySK ERP	DrugFirmC in CountryAU ERP	DrugFirmC in CountryBG ERP	DrugFirmC in CountryPL ERP	DrugFirmC in CountryLV ERP	DrugFirmC in CountryHU ERP	DrugFirmC in CountrySK ERP
0																		
0.5																		
1																		
1.5	10	10	10	10	10	10												
2	10	10	10	10	10	10												
2.5	10	10	10	10	10	10												
3	10	10	10	10	10	10												
3.5	10	10	10	10	10	10												
4	10	10	10	10	10	10												
4.5	10	10	10	10	10	10												
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5.5	10	10	10	10	10	10												
6	10	10	10	10	10	10												
6.5	10	10	10	10	10	10												
7	10	10	10	10	10	10												
7.5	10	10	10	10	10	10												
8	10	10	10	10	10	10												
8.5	10	10	10	10	10	10												
9	10	10	10	10	10	10												
9.5	10	10	10	10	10	10	9	9	9	9	9	9						
10	10	10	10	10	10	10	9	9	9	9	9	9						
10.5	9	9	9.225	9.143	10	9	9	9	9	9	9	9	8	8	8	8	8	8
11	9	9	9.225	9.143	10	9	9	9	9	9	9	9	8	8	8	8	8	8
11.5	8.1	8.1	8.303	8.261	9	9	9	9	8.1	9	9	8.1	8	8	8	8	8	8
12	8.1	8.1	8.303	8.261	9	8.1	9	9	8.1	9	9	8.1	8	8	8	8	8	8
12.5	8.1	7.29	7.78	7.853	8.1	7.29	8.1	7.29	7.776	8.013	8.1	8.1	8	8	8	8	8	8
13	8.1	7.29	7.78	7.853	8.1	7.29	8.1	7.29	7.776	8.013	8.1	7.29	8	8	8	8	8	8
13.5	7.29	7.29	7.78	7.606	8.1	7.29	7.29	6.561	7.776	7.068	8.1	6.561	8	8	7.2	8	7.2	7.2
14	7.29	7.29	7.78	7.606	8.1	6.561	7.29	6.561	7.776	7.068	8.1	6.561	8	8	7.2	8	7.2	7.2
14.5	7.29	6.561	7.07	6.966	7.29	6.561	7.29	5.905	6.914	7.06	7.29	6.561	8	7.2	7.452	7.383	7.2	7.2
15	7.29	6.561	7.07	6.966	7.29	6.3	7.29	5.905	6.914	7.06	7.29	5.905	8	7.2	7.452	7.383	7.2	6.48
15.5	7.29	6.3	6.363	6.998	7.29	5.67	6.561	5.314	6.914	6.917	6.561	5.905	8	6.48	6.707	7.226	7.2	6.48
16	7.29	6.3	6.363	6.998	7.29	5.67	6.561	5.314	6.914	6.917	6.561	5.314	8	6.48	6.707	7.226	7.2	5.832
16.5	7.29	5.103	6.154	6.236	6.561	5.103	6.561	5.314	6.133	6.356	6.561	5.314	8	5.249	6.597	6.778	7.2	5.249
17	7.29	5.103	6.154	6.236	6.561	5.103	6.561	5.314	6.133	6.356	6.561	5.314	8	5.249	6.597	6.778	7.2	5.249
17.5	7.29	5.103	5.539	6.205	6.561	5.103	5.905	4.783	6.133	5.678	5.905	4.783	8	5.249	6.597	6.83	7.2	5.249
18	7.29	5.103	5.539	6.205	6.561	5.103	5.905	4.783	6.133	5.678	5.905	4.783	8	5.249	6.597	6.83	7.2	5.249
18.5	6.561	5.103	5.826	5.72	5.905		5.905	4.305	5.504	5.788	5.905	4.783	8	4.724	6.16	6.382	7.2	4.724
19	6.561	5.103	5.826	5.72	5.905		5.905	4.305	5.504	5.788	5.905	4.305	8	4.724	6.16	6.382	7.2	4.724
19.5	6.561		5.244	5.763	5.314		5.314		5.504	5.487	5.905	4.305	8	4.724	6.16	6.267	7.2	4.724
20	6.561		5.244	5.763	5.314		5.314		5.504	5.487	5.905	5.314	8	4.724	6.16	6.267	7.2	4.252
20.5	5.905		5.513	5.39	5.314		5.314		5.128	5.269	5.314	4.783	8	4.252	5.705	5.789	7.2	4.252
21	5.905		5.513	5.39	5.314		5.314		5.128	5.269	5.314	4.783	8	4.252	5.705	5.789	7.2	4.252
21.5	5.314						5.314		5.128	4.666	5.314	4.783	8	4.252	5.705	5.777	7.2	4.252

	DrugFirmA in CountryAU PT ERP	DrugFirmA in CountryBG PT ERP	DrugFirmA in CountryPL PT ERP	DrugFirmA in CountryLV PT ERP	DrugFirmA in CountryHU PT ERP	DrugFirmA in CountrySK PT ERP	DrugFirmB in CountryAU PT ERP	DrugFirmB in CountryBG PT ERP	DrugFirmB in CountryPL PT ERP	DrugFirmB in CountryLV PT ERP	DrugFirmB in CountryHU PT ERP	DrugFirmB in CountrySK PT ERP	DrugFirmC in CountryAU PT ERP	DrugFirmC in CountryBG PT ERP	DrugFirmC in CountryPL PT ERP	DrugFirmC in CountryLV PT ERP	DrugFirmC in CountryHU PT ERP	DrugFirmC in CountrySK PT ERP
0																		
0.5																		
1																		
1.5	10	10	10	10	10	10												
2	10	10	10	10	10	10												
2.5	10	10	10	10	10	10												
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11	9	9	9.119	9	10	9	9	9	9	9	9	9	8	8	8	8	8	8
11.5	8.1	8.1	8.207	8.112	9	8.1	9	9	8.1	9	9	8.1	8	8	8	8	8	8
12	8.1	8.1	8.207	8.112	9	8.1	9	9	8.1	9	9	8.1	8	8	8	8	8	8
12.5	8.1	7.29	7.814	7.922	8.1	8.1	8.1	7.29	7.698	7.897	8.1	7.29	8	7.2	7.953	7.886	8	8
13	8.1	7.29	7.814	7.922	8.1	7.29	8.1	7.29	7.698	7.897	8.1	7.29	8	7.2	7.953	7.886	8	7.2
13.5	8.1	6.561	7.814	7.804	8.1	7.29	8.1	6.561	7.698	6.914	8.1	7.29	7.2	7.2	7.158	7.856	8	7.2
14	8.1	6.561	7.814	7.804	8.1	6.561	8.1	6.561	7.698	6.914	8.1	6.561	7.2	7.2	7.158	7.856	8	6.48
14.5	8.1	6.561	7.157	7.035	7.29	6.561	7.29	5.905	6.95	6.86	7.29	6.561	7.2	6.48	7.268	7.294	8	6.48
15	8.1	6.561	7.157	7.035	7.29	6.561	7.29	5.905	6.95	6.86	7.29	5.905	7.2	6.48	7.268	7.294	8	6.48
15.5	7.29	5.905	7.157	7.035	7.29	5.905	7.29	5.314	6.95	6.86	7.29	5.905	7.2	6.48	6.541	7.294	8	5.832
16	7.29	5.905	7.157	7.035	7.29	5.905	7.29	5.314	6.95	6.86	7.29	5.314	7.2	6.48	6.541	7.294	8	5.832
16.5	7.29	5.314	6.605	6.603	7.29	5.905	7.29	5.314	6.253	6.521	6.561	5.314	7.2	5.249	6.519	6.723	8	5.249
17	7.29	5.314	6.605	6.603	7.29	5.314	7.29	5.314	6.253	6.521	6.561	5.314	7.2	5.249	6.519	6.723	8	5.249
17.5	7.29	5.314	6.605	5.806	6.561		6.561	4.783	6.253	6.39	6.561	4.783	7.2	5.249	5.867	6.618	8	5.249
18	7.29	5.314	6.605	5.806	6.561		6.561	4.783	6.253	6.39	6.561	4.783	7.2	5.249	5.867	6.618	8	5.249
18.5	7.29		6.25	6.033	6.561		5.905	4.783	5.542	5.818	5.905	4.783	7.2	4.724	6.062	6.228	8	4.724
19	7.29		6.25	6.033	6.561		5.905	4.783	5.542	5.818	5.905	4.783	7.2	4.724	6.062	6.228	8	4.724
19.5	6.561		6.25	6.206	5.905		5.905	4.305	5.542	5.656	5.314	4.305	7.2	4.724	5.455	6.242	7.2	4.724
20	6.561		6.25	6.206	5.905		5.905	4.305	5.542	5.656	5.314	4.305	7.2	4.724	5.455	6.242	7.2	4.724
20.5	6.561		5.855	5.622	5.905		5.905	4.305	5.036	5.137	5.314	4.305	7.2	4.252	5.696	5.909	7.2	4.252
21	6.561		5.855	5.622	5.905		5.905	4.305	5.036	5.137	5.314	4.305	7.2	4.252	5.696	5.909	7.2	4.252

Figure 9.3.2.a Appendix A No ERP scenario, Parallel Trade vs No Parallel Trade (all EU countries)

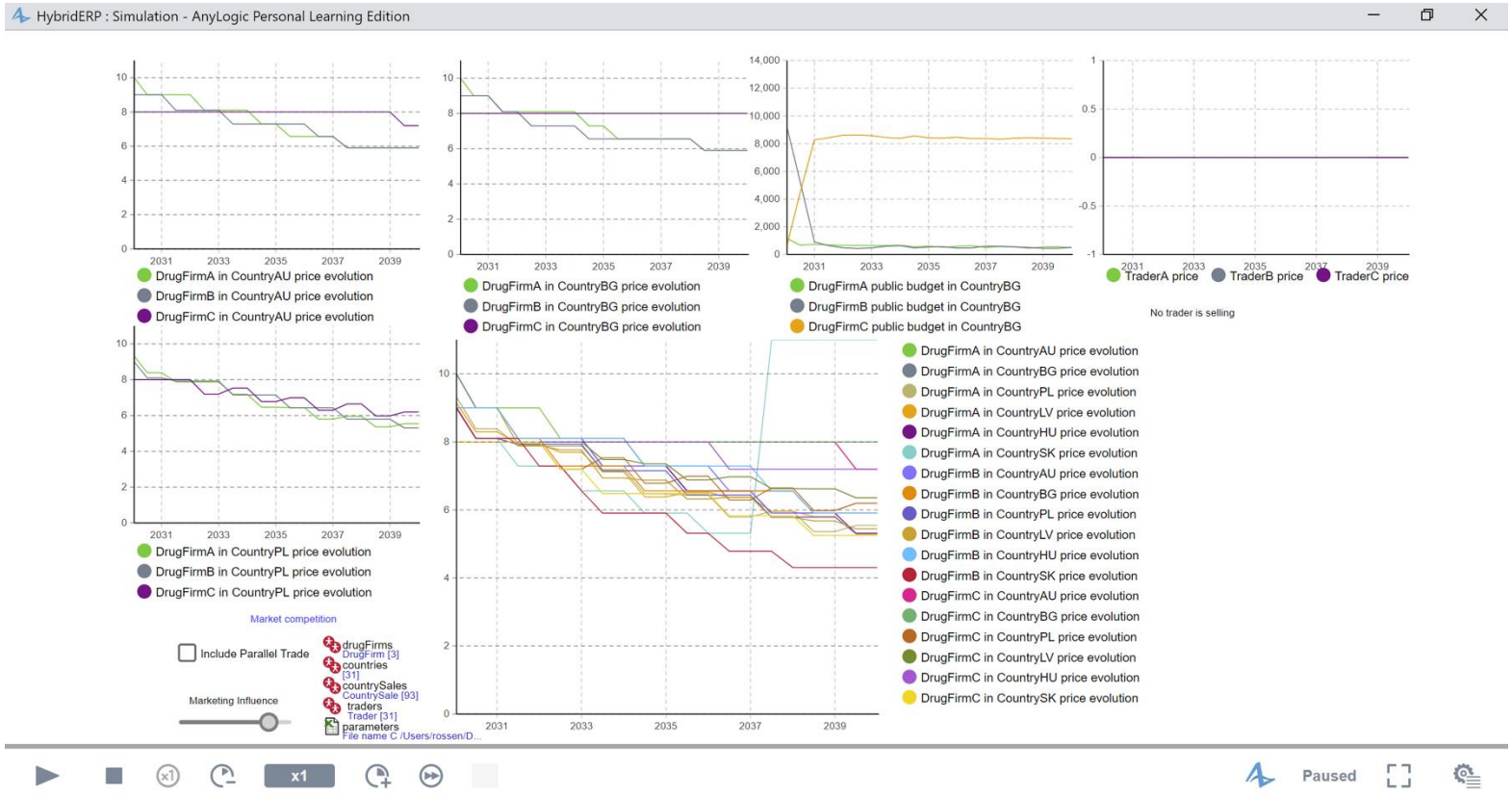
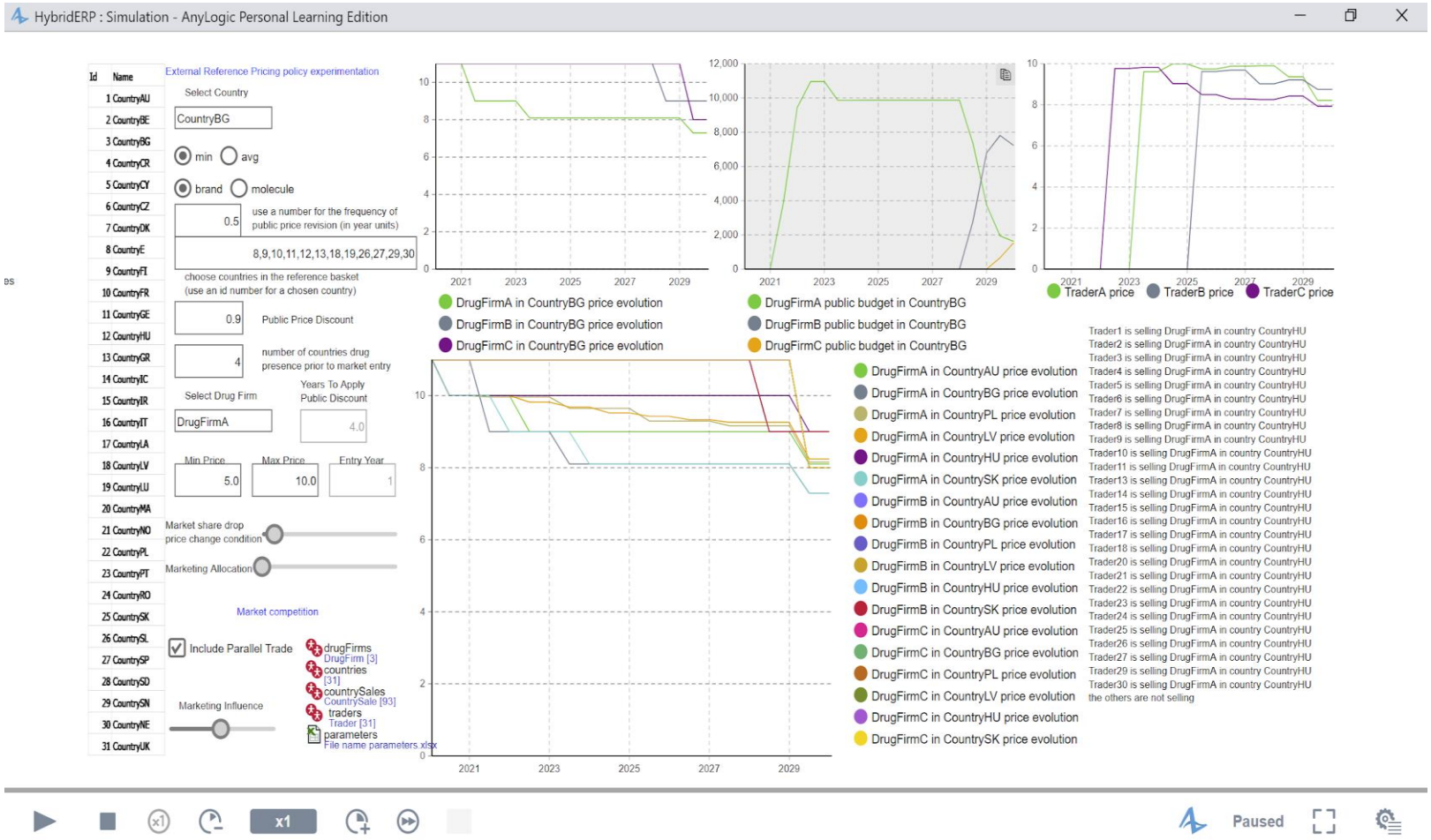


Figure 9.3.2.b Appendix A No ERP with Parallel Trade

Figure 9.3.4 Appendix A Public policy scenario user dashboard configured for specific local market



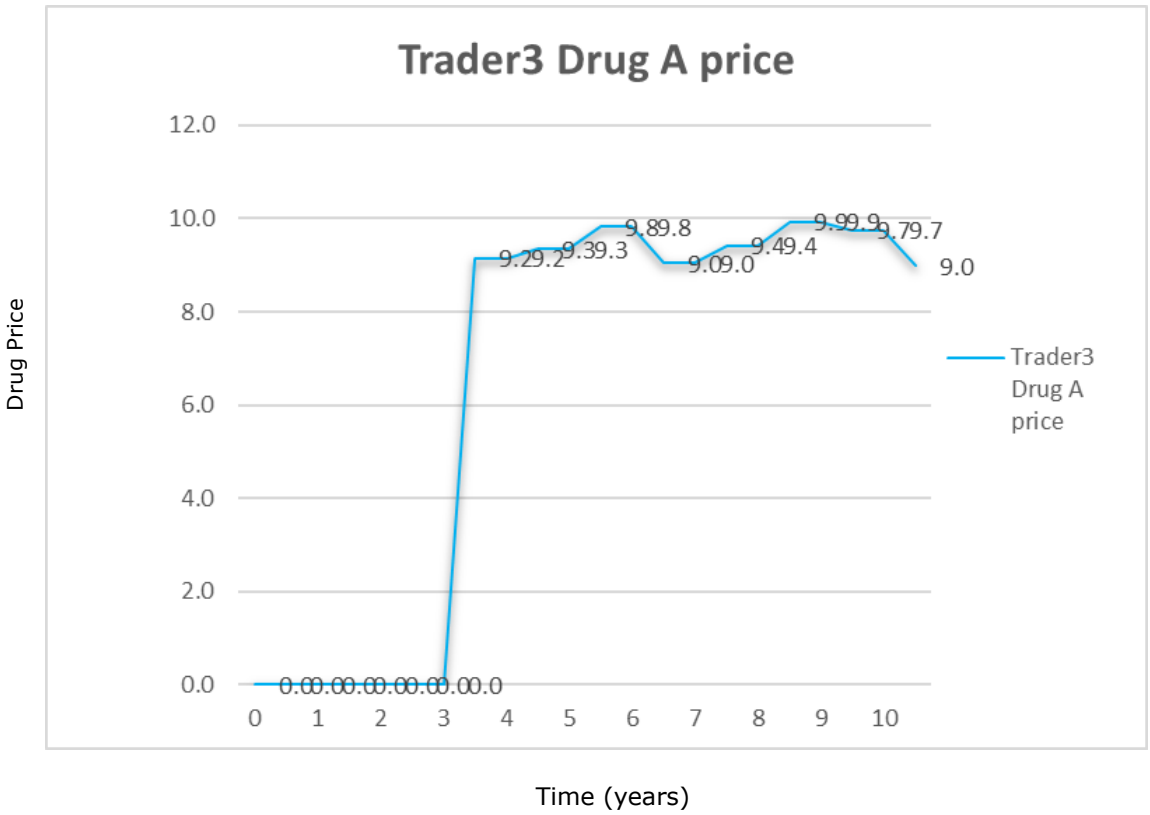


Figure 9.2.6.2 Appendix A Drug A selling price for one parallel trading agent

Figure 9.2.7.2 Appendix A Parallel Traders Drug A Price

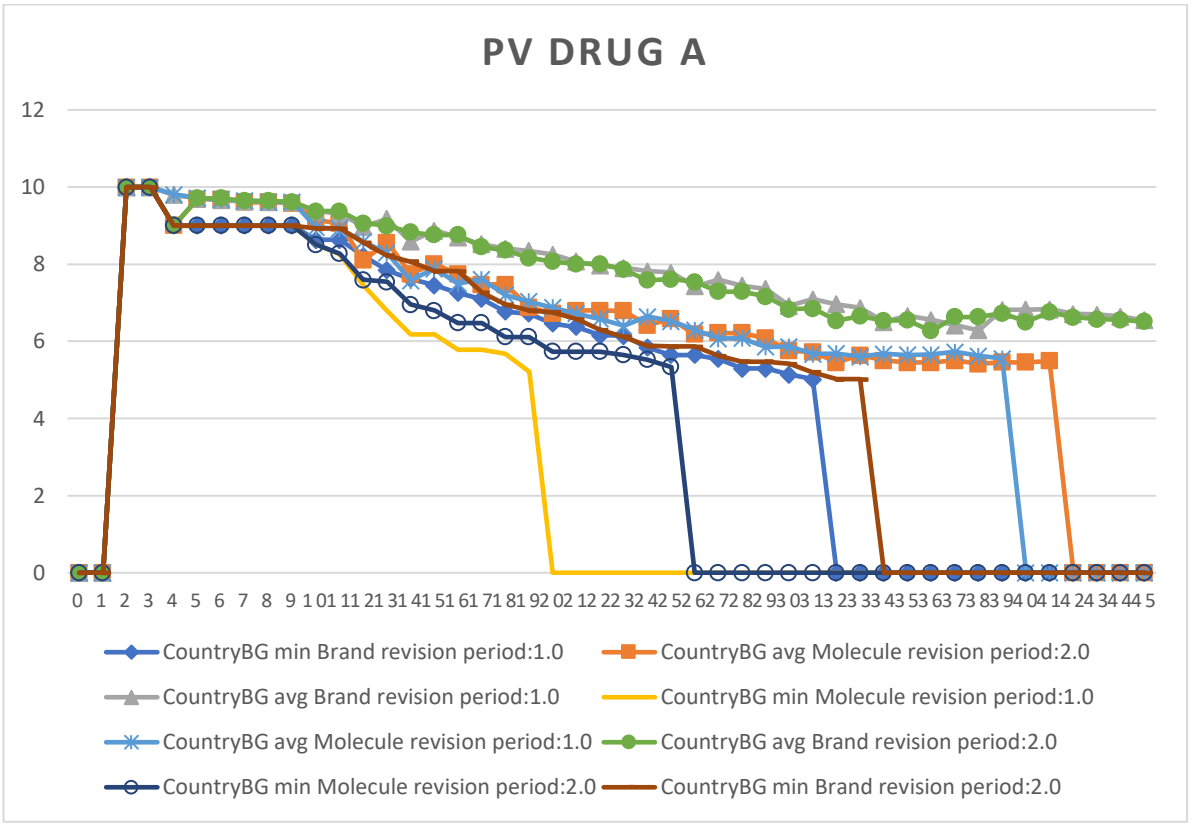


Figure 9.3.7.I Appendix A Parameter variation for original drug A: ERP on 'min', ERP on 'avg', revision period of one or two years and prescribing on 'brand' or ''molecule'

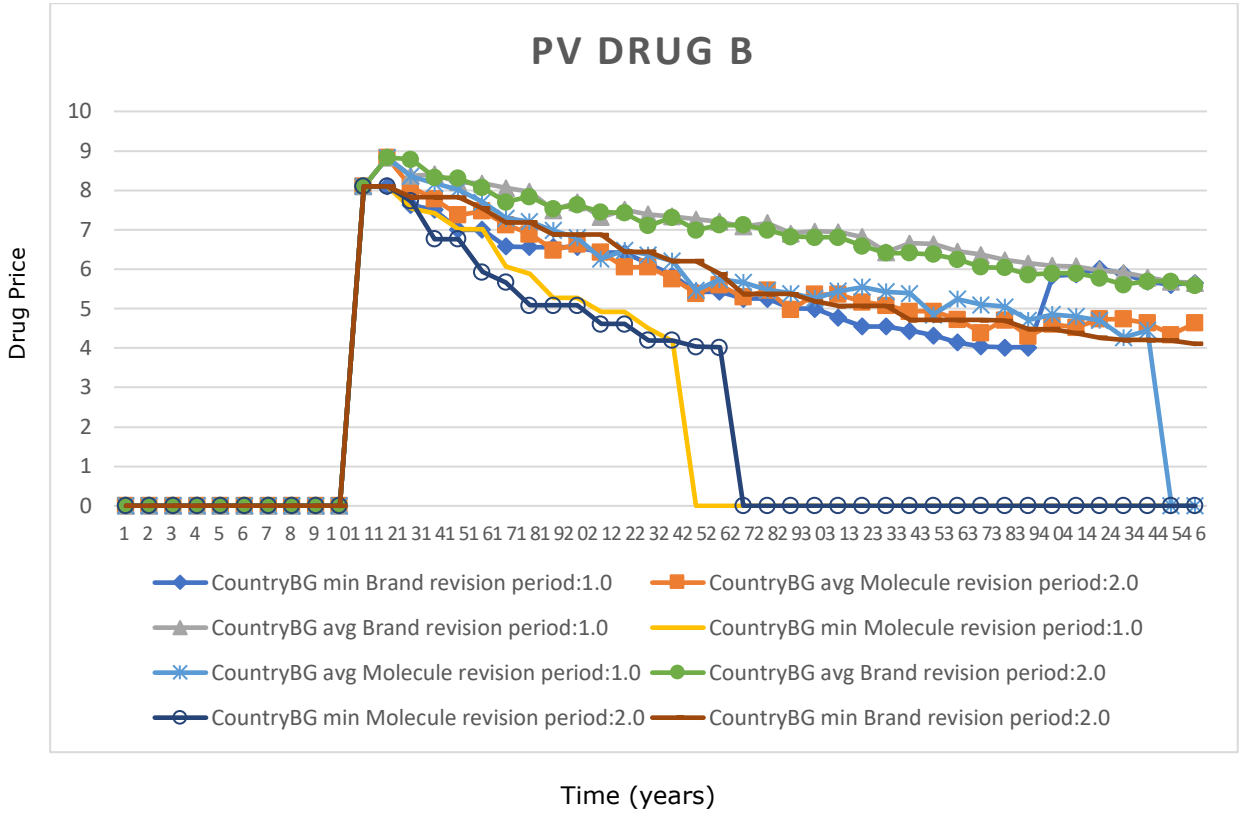


Figure 9.3.7.II Appendix A Parameter variation for generic drug B: ERP on 'min', ERP on 'avg', revision period of one or two years and prescribing on 'brand' or ''molecule'

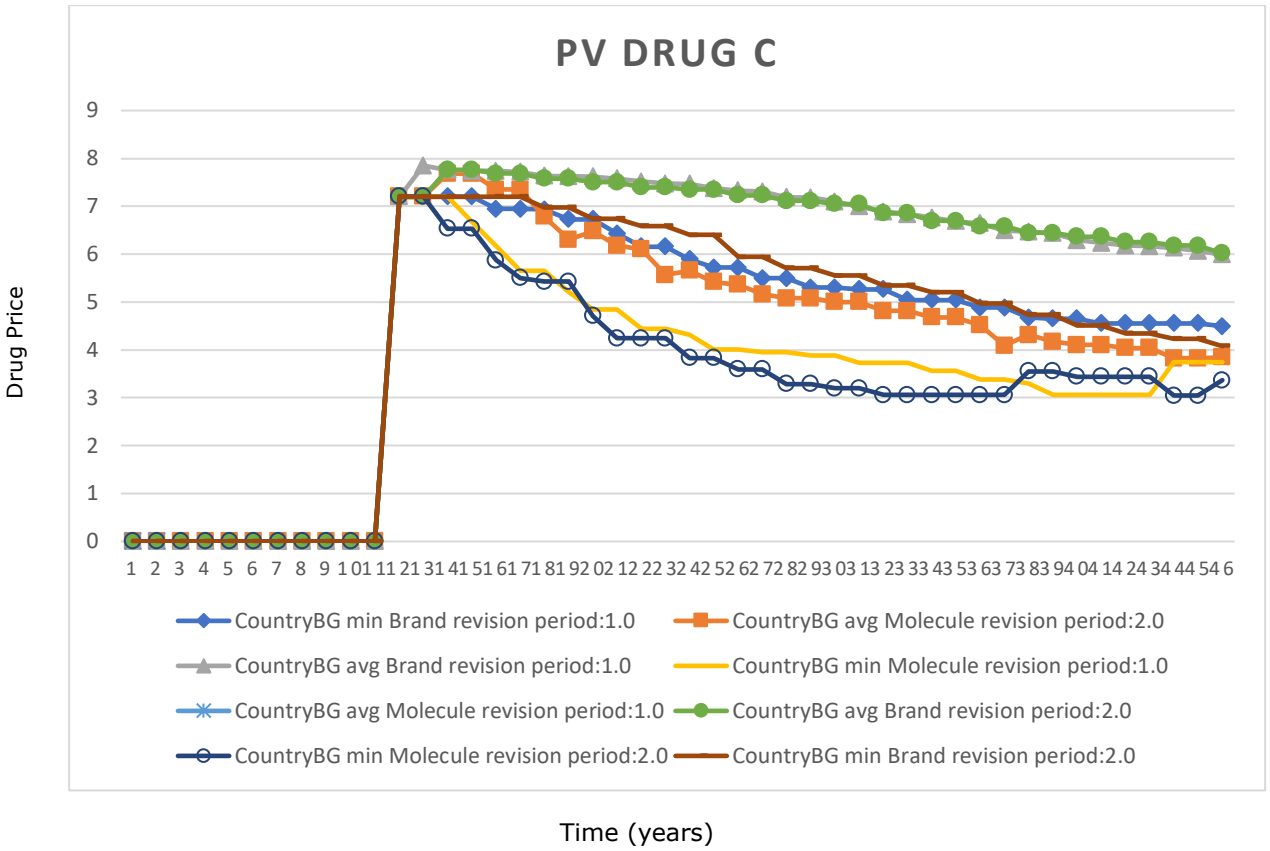


Figure 9.3.7.III Appendix A Parameter variation for generic drug C: ERP on 'min', ERP on 'avg', revision period of one or two years and prescribing on 'brand' or ''molecule'

Figure 9.3.10.1.a Appendix A Parameter variation experiment for drug A scenario for Bulgaria "with ERP", 100 runs for "brand" prescribing and 100 runs "molecule" prescribing, ERP price calculation on "min", 1 year period for drug price revisions, with parallel traders

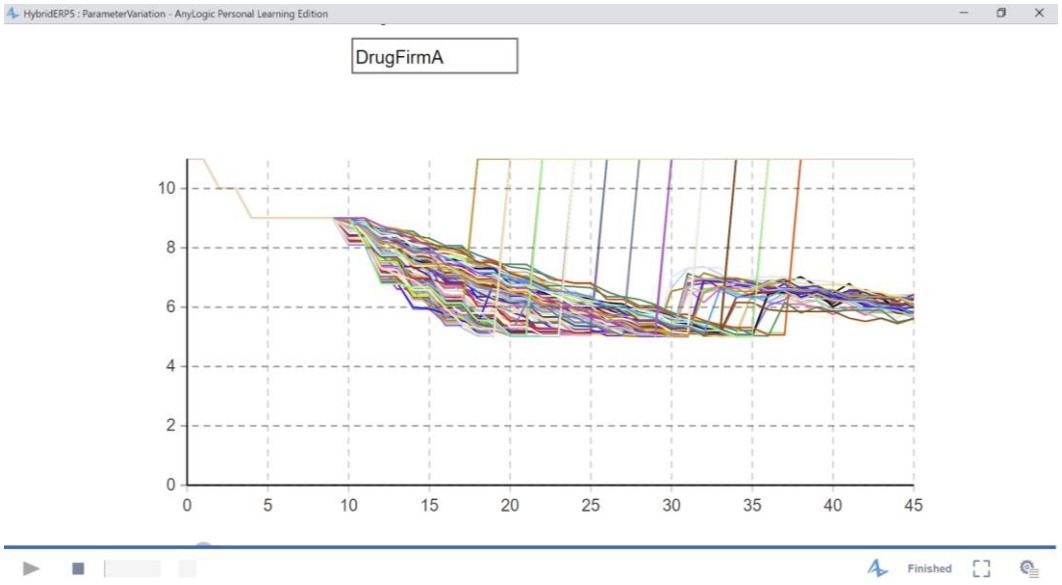


Figure 9.3.10.1.b Appendix A Parameter variation experiment for drug A scenario for Bulgaria "no ERP", 100 runs for "brand" prescribing and 100 runs "molecule" prescribing, ERP price calculation on "min", 1 year period for drug price revisions, with parallel traders

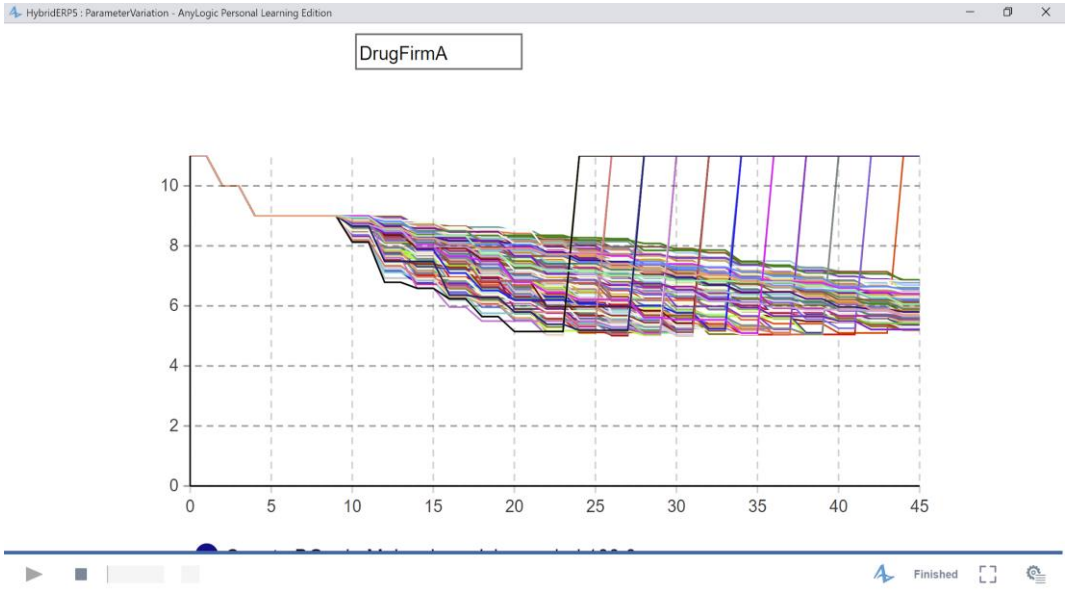


Figure 9.3.10.3.a Appendix A Parameter variation experiment for drug B scenario for Bulgaria "with ERP", 100 runs for "brand" prescribing and 100 runs "molecule" prescribing, ERP price calculation on "min", 1 year period for drug price revisions, with parallel traders

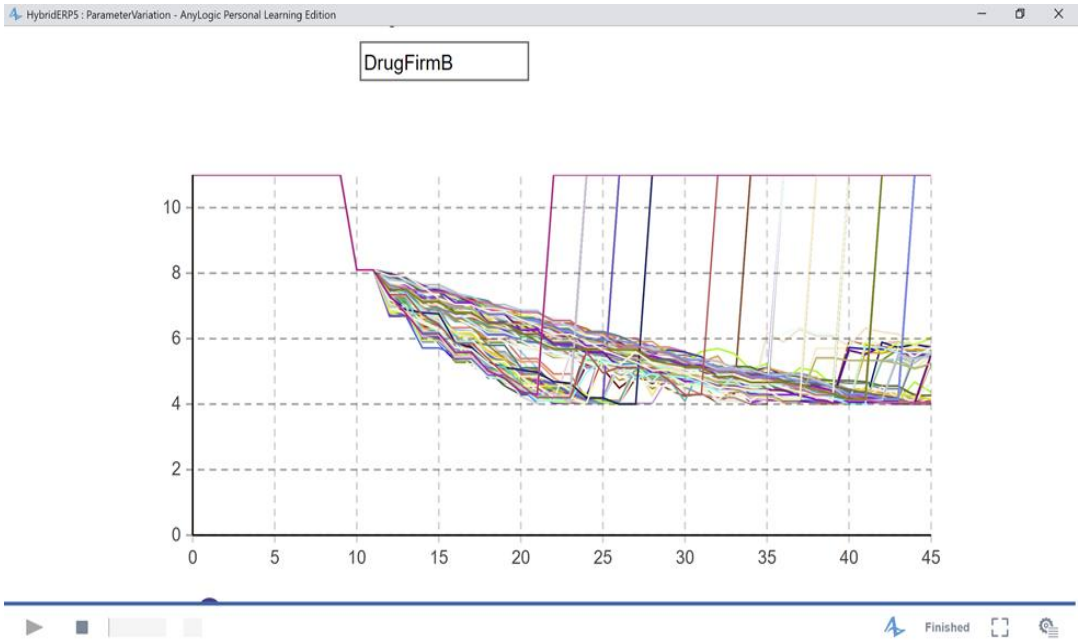


Figure 9.3.10.3.b Appendix A Parameter variation experiment for drug B scenario for Bulgaria "no ERP", 100 runs for "brand" prescribing and 100 runs "molecule" prescribing, ERP price calculation on "min", 1 year period for drug price revisions, with parallel traders

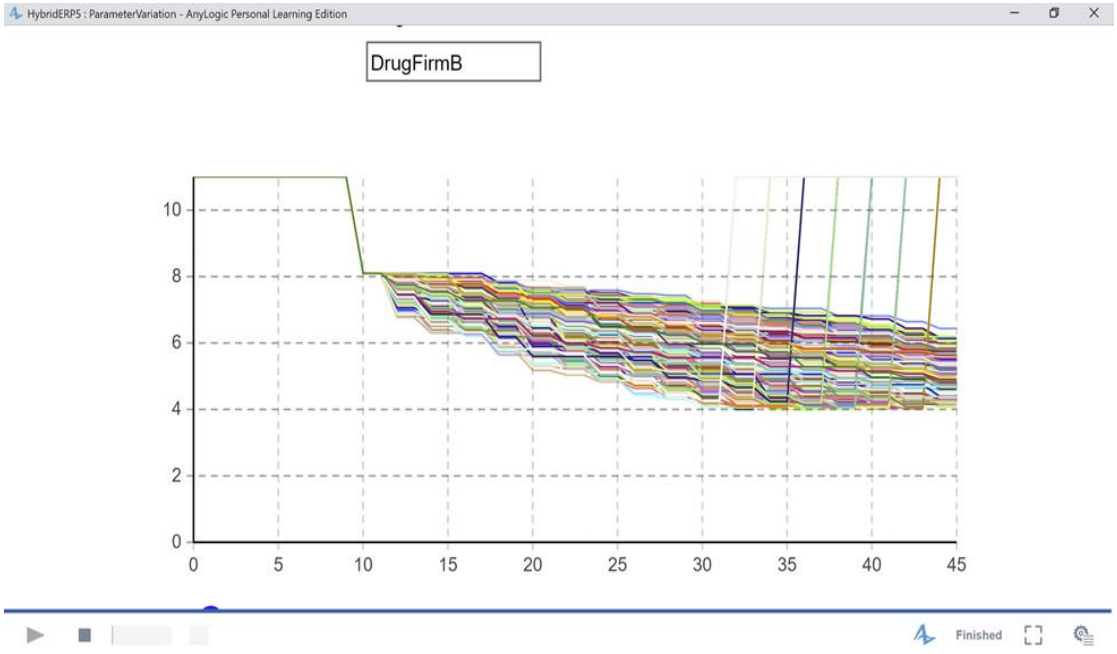


Figure 9.3.10.4.a Appendix A Parameter variation experiment for drug C scenario for Bulgaria "with ERP", 100 runs for "brand" prescribing and 100 runs "molecule" prescribing, ERP price calculation on "min", 1 year period for drug price revisions, with parallel traders

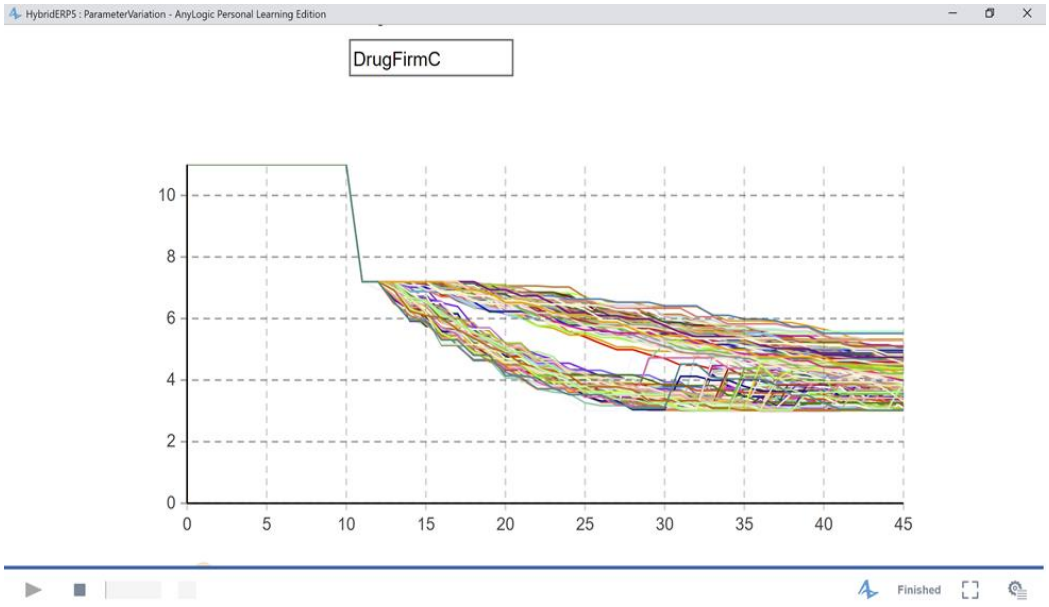
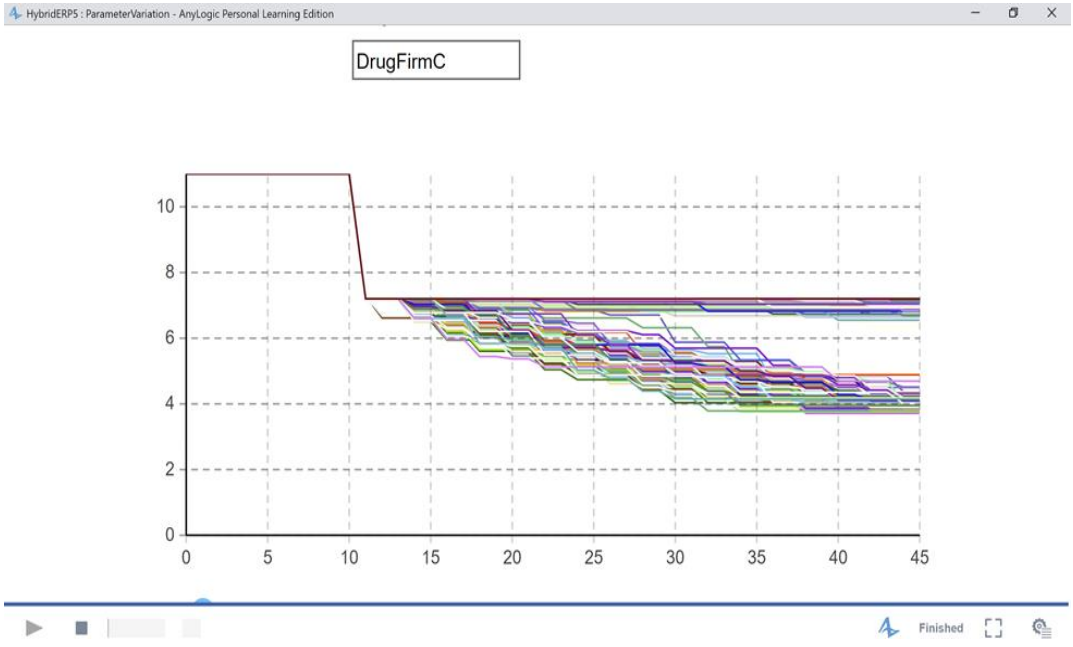


Figure 9.3.10.4.b Appendix A Parameter variation experiment for drug C scenario for Bulgaria "no ERP", 100 runs for "brand" prescribing and 100 runs "molecule" prescribing, ERP price calculation on "min", 1 year period for drug price revisions, with parallel traders



Scenario PT MEPD brand or molecule, price calculation on avg, price revision period one year

Figure 9.3.10.5.a Appendix A Parameter variation experiment for drug A scenario for Bulgaria "no ERP", 100 runs for "brand" prescribing and 100 runs "molecule" prescribing, ERP price calculation on "avg", 1 year period for drug price revisions, with parallel traders

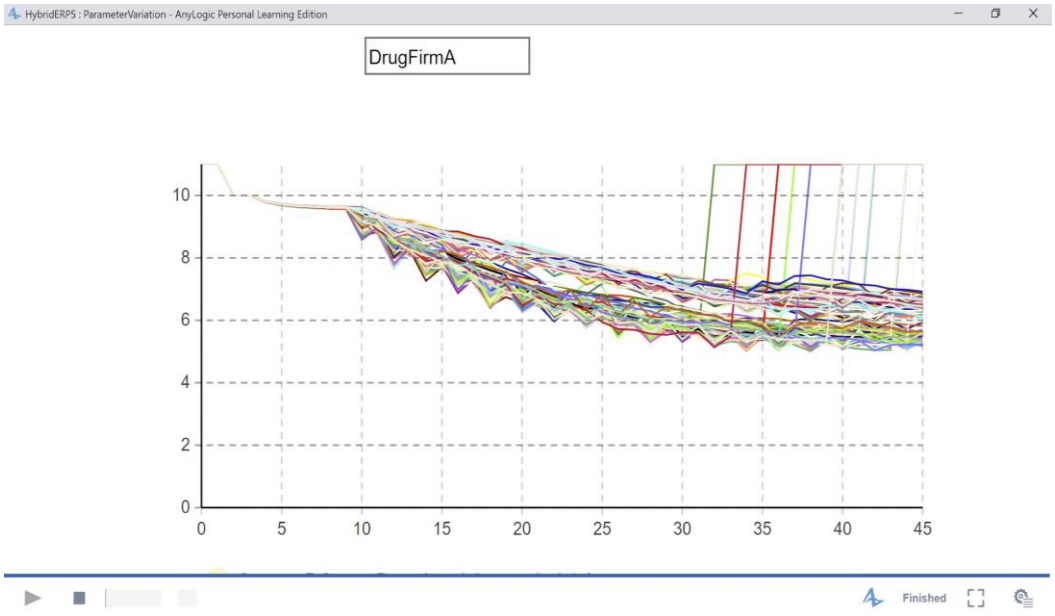


Figure 9.3.10.5.b Appendix A Parameter variation experiment for drug B scenario for Bulgaria "no ERP", 100 runs for "brand" prescribing and 100 runs "molecule" prescribing, ERP price calculation on "avg", 1 year period for drug price revisions, with parallel traders

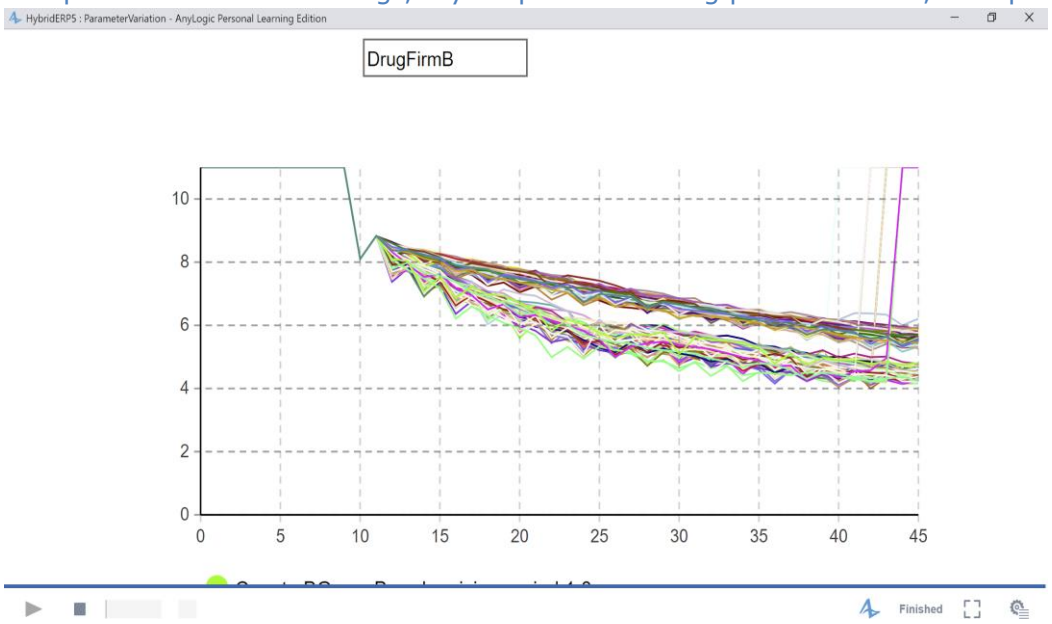
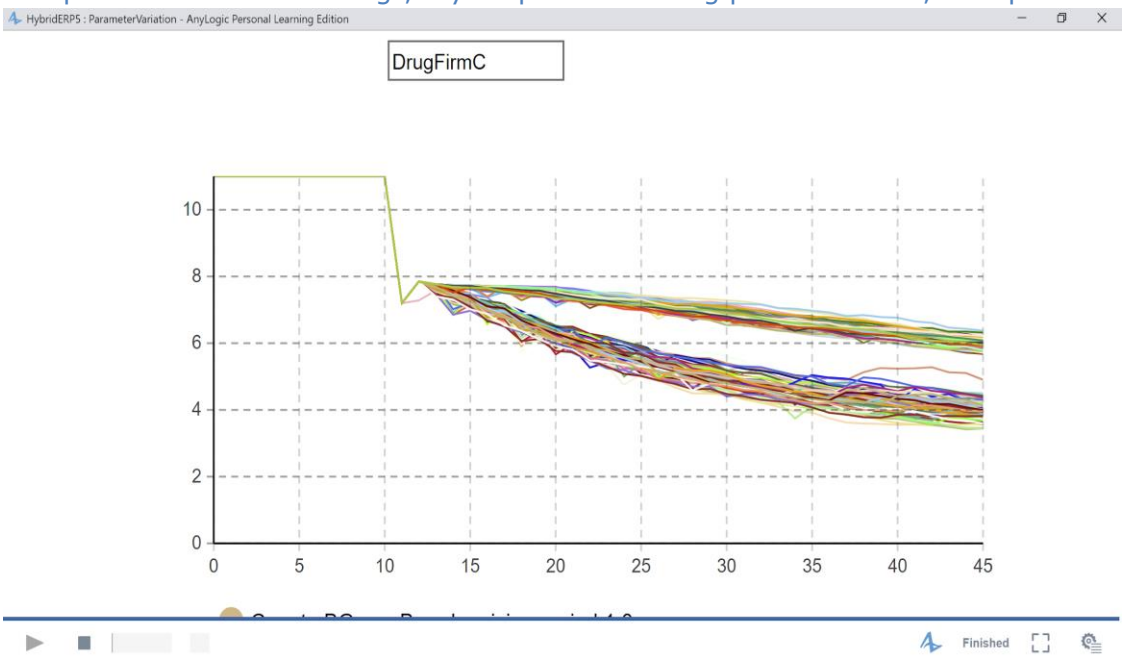


Figure 9.3.10.5.c Appendix A Parameter variation experiment for drug C scenario for Bulgaria "no ERP", 100 runs for "brand" prescribing and 100 runs "molecule" prescribing, ERP price calculation on "avg", 1 year period for drug price revisions, with parallel traders



ERP scenario and PV experiments analysis in Excel, related to Chapter IX


ERP Experiment PV table (version 1) grapl


ERP Experiment PV table-P1 graph drug E


ERP Experiment PV table-P graph drug C


ERP Experiment all EU.xlsx


ERP experiment avg ERP1ABC P.xlsx

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