



The Impact of External Reference Pricing within and across Countries

Panos Kanavos

Anna-Maria Fontrier

Jennifer Gill

Olina Efthymiadou

Nicola Boekstein

London School of Economics
Houghton Street
London
England
WC2A 2AE

Website: www.lse.ac.uk

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List of Acronyms

BMI	Business Monitor International
CRD	Centre for Reviews and Dissemination
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGA	European Generic Medicines Associations
ERP	External Reference Pricing
EU	European Union
GDP	Gross Domestic Product
GOEG	Gesundheit Österreich GmbH
HICs	High Income Countries
HiT	Health Systems in Transition
IMS	Intercontinental Marketing Services
LICs	Low Income Countries
MA	Marketing Authorisation
N/A	Not Applicable
OECD	Organisation for Economic Cooperation and Development
POM	Prescription Only Medicine
PPP	Purchasing Power Parity
PPRI	Pharmaceutical Pricing and Reimbursement Information
R&D	Research and Development
RCT	Randomized Controlled Trial
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation
WHO CC	World Health Organisation Collaboration Centre
WoS	Web of Science

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ABSTRACT

OBJECTIVES

External Reference Pricing (ERP) is widely used to regulate drug prices and help determine reimbursement. Although the literature has largely focused on the impact of ERP on a number of policy endpoints (e.g. pharmaceutical prices and spending, launch sequencing or price convergence, among others), as well as its impact from a geographical perspective (e.g. Europe or the Middle East), a comparative study drawing on evidence from different settings – developed, emerging and developing – and across a range of policy variables does not exist to date. The objective of this paper is to critically appraise the impact of ERP systems as they are applied in different settings on selected health-system outcomes internationally.

METHODS

A systematic literature review using a keyword strategy was conducted both in the peer review and grey literature from 2000 to 2015. The endpoints studied were the impact of ERP: first, at a national level, notably on (a) pharmaceutical cost-containment (decreased pharmaceutical expenditure); (b) price levels for prescription medicines; (c) pharmaceutical utilisation; (d) availability; (e) affordability; (f) equity; (g) efficiency; (h) industrial policy; and, second, at an international level, specifically on (a) price stability; (b) price convergence; and on (c) launch sequencing and delays.

RESULTS

547 studies were identified with relevant titles and abstracts, 76 of which were included in the analysis. Of these, ten were empirical using a clear methodological design, resulting in good quality evidence, whereas the rest of the identified papers were descriptive studies using a post-only design when examining some endpoints, resulting in low quality and weak strength of evidence. The evidence at national level suggests that, while ERP can contribute to pharmaceutical cost-containment, in terms of pricing level, this is only a short-term effect, lasting between one to two years, and might undermine the availability and affordability of medicines. Evidence

also suggests that downward price convergence and reduced revenues for manufacturers that can arise as a consequence of ERP in a number of settings can be detrimental to investment in innovation. ERP does not seem to promote efficiency in achieving country-specific health system goals, although the evidence on this is weak. Within-country list price levels are influenced predominantly by the features of ERP systems, particularly the type of basket countries and re-pricing frequency. Across countries, there is evidence that ERP may cause spillover effects, such as launch delays, price instability, and list price convergence; however, price differences across countries are still observed due to the different nature of the markets and the ERP formula considered in the ERP design of each country. It has also been argued that reduced revenues associated with ERP might present a disinvestment criterion towards industry innovation. Launch delays vary significantly across countries; but any launch delays in particular settings cannot be attributed wholly to ERP, as launching a new product is also dependent on other factors such as country income level, country market size, launch sequencing by the manufacturers and other pricing regulations and bureaucratic processes implemented along with ERP.

CONCLUSIONS

According to our findings, ERP has not regulated price control efficiently and has unintended consequences that reduce its beneficial impact. However, if ERP is carefully designed with minimal price revisions, prudent selection of basket size and countries, and consideration of the actual transaction prices, including any possible discounts, then it could serve as a more effective cost-containment mechanism. Still, it would be highly unlikely for ERP to contribute on its own to volume control, unless supplemented by demand-side measures. Considering the aforementioned conditions, ERP has the potential to enhance welfare and equitable access to medicines across countries and to potentially promote industry innovation in the context of defining the basket of comparators (i.e. inclusion of countries that explicitly recognize value and the “value of innovation”).

EXECUTIVE SUMMARY

BACKGROUND

External Reference pricing (ERP) is a powerful tool implemented by government policy makers that is used extensively across the world, either to inform or set pharmaceutical prices in a given country. Its value is generally judged against its ability to deliver government policy goals. ERP systems differ substantially in the way that they are implemented in different countries. Even though the literature has focused extensively on studying various ERP designs, there is an identifiable gap in the existing evidence about the quantifiable impact of ERP on various policy objectives within and across countries.

This study aims to gain a clearer understanding of the impact of ERP systems on important health system goals such as availability, affordability and diffusion/utilisation of pharmaceuticals; it also aims to analyse the impact that ERP systems have at the domestic and international levels, particularly considering their likely spillover effects.

METHODOLOGY

A systematic literature review was conducted, conforming to the guidelines for systematic reviews. The endpoints studied were the impact of ERP: first, at a national level, notably on (a) pharmaceutical cost-containment; (b) price levels for prescription medicines; (c) utilisation of pharmaceuticals; (d) availability; (e) affordability; (f) equity; (g) efficiency; and (h) industrial policy; and, subsequently, at an international level, specifically on (a) price stability; (b) price convergence; (c) launch sequencing and delays; and on (d) potential spillover effects.

Several databases were searched using a keyword strategy for both peer-reviewed and grey literature published between 2000 and 2015. In addition to the systematic literature reviews, a targeted search of the WHO, the WHOCC-GOEG and the OECD online databases was carried out to ensure that no relevant reports were overlooked. An excel spreadsheet was used to extract the relevant information on each endpoint from the final set of papers included in the study; and a subsequent synthesis of the literature evidence was carried out to identify key trends and relationships regarding the impact of ERP policies in different countries or geographical regions.

The impact assessment studies in pharmaceutical policy were found to be weak, usually focusing on the short-term impact only. The quality and the strength of evidence found in the literature and used in this systematic literature review was critically assessed. The number of studies analysing the short and/or long-term impact of ERP against the selected endpoints was also recorded.

RESULTS

Impact of ERP at country level

The evidence yielded from the results of this systematic literature review at a national level suggests that ERP has generated **healthcare savings**, at least in the short-term, but the extent of the savings generated depended largely on the methodology of the implemented ERP and on any other pharmaceutical policies in effect within the studied setting.

Across Europe, ERP was shown to have reduced **pharmaceutical prices**. However, the price decreases were also shown to be dependent on the design of ERP and on the characteristics of the market within which it was being implemented.

Evidence also suggests that ERP leads to downward price convergence across countries and to reduced revenues for manufacturers. ERP may not only be detrimental in terms of the **availability** of medicines within a country, but also discourages manufacturers from investing in **industrial innovation**. Furthermore, the emerging theme from the current literature is that ERP does not seem to promote **efficiency**, as ERP does not typically reflect the goals and priorities of the health system in which it operates. ERP may shift the welfare equilibrium within a country due to higher pricing relative to country income with subsequent **affordability** issues as a consequence. On the other hand, it cannot directly control **drug consumption** since this is a factor also influenced by other external demand and/or supply side variables. However, any assessment of the national-level impact of ERP must be analysed on a system-wide basis due to the interconnectedness of the key endpoints.

Impact of ERP across countries

The evidence gathered at the international level was extensive, examining the spillover effects and their impact across countries. The overall quality and the strength of the evidence found on the impact of ERP across countries was low as empirical evidence was provided by studies with weak methodological design, focusing mostly on the short-term effects of ERP. Overall, as the majority of countries reference each other when calculating the external referencing price, **spillover effects** have found to have an impact on individual country prices, causing unexpected consequences in countries applying ERP and leading to launch delays. These **launch delays** vary considerably from country to country, depending on various determinants such as the country's income, the size of the market and the regulation setting, as well as the price levels that can be modified by manufacturers via launch sequencing. ERP can potentially lead to **price instability** across countries as prices have been found to fluctuate due to a variety of reasons, such as the market characteristics, the design of ERP, including frequency of price revisions and basket size, and other regulations applied in each country. In addition, while the ability of ERP to **harmonize prices** across countries has been recorded throughout the literature, pricing differentials between countries are also observed.

POLICY IMPLICATIONS

According to the available evidence around the impact of ERP within a country's borders, we conclude that ERP might have an impact on health system specific goals. At the international level, ERP has an impact across countries, causing unwanted spillover effects, price convergence, price instability and launch delays.

As observed throughout the literature the impact of ERP on a country will affect the countries using the studied country as a reference and vice versa. However, the impact of ERP at both the national and international level depends largely on the

ERP design of both the studied and the referenced country as well as other exogenous factors, such as other pricing mechanisms implemented in individual countries. In addition, ERP is characterised by "path dependence", meaning that the features of the ERP system influence the overall outcome both within and across countries.

Overall, as presented in Tables 15 and 16, the available evidence on the impact of ERP within and across a country's borders is classified by the authors as relatively weak in terms of quality, as it emerged from only a limited number of empirical studies (10 out of 76 studies included in total), the majority of which were based on qualitative analyses of survey data or regression analyses of observational data, which could not be controlled for bias and/or potential confounders by the authors. No relevant studies were found that assessed or quantified the impact of ERP by employing compelling econometric methodological designs, such as time series or pre-post analyses.

CONCLUSIONS

Based on the evidence presented in this study, we can anticipate that ERP, in its current state has not been the optimal pricing policy for maximising the efficiency of health systems in terms of managing prices, optimising drug consumption and delivering equitable, affordable access to medicines, although the poor quality of existing evidence prevents us from drawing a clear picture on the extent to which ERP might undermine the above government policy goals within and across countries. Changing the design of the ERP system, by increasing the frequency of price revisions and by providing a tailor-made ERP methodology for each country may lead to lower pharmaceutical prices within the country, however such changes could have a detrimental effect on the attainment of other policy goals. Unquestionably, there is an unmet need both on how ERP systems should be designed in order to attain an impact of ERP on a number of policy goals within and across countries and on quantifying its impact.

1. INTRODUCTION

External Reference Pricing (ERP) is used widely in Europe, Latin America, Southeast and East Asia, Africa and the Middle East to inform decisions on pricing and coverage of pharmaceuticals by health insurance systems. ERP is used either as the dominant method to explicitly set prices or as one of the criteria to inform pricing and reimbursement decisions. On-patent prescription pharmaceuticals, imported pharmaceuticals and reimbursable pharmaceuticals are most likely to be included in ERP systems (Espin et al. 2014, Toumi et al. 2014, Leopold et al. 2012, Europe Economics 2013, Rémuzat et al. 2015 and European Commission 2015).

WHO defines external price referencing 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” (WHO 2013). ERP is often considered to be a powerful tool that influences prices at a national level, but also at an international level, due to the interlinking of prices and path dependency (Leopold et al. 2012; Marinoso et al. 2011, Espin et al. 2014; and Houy and Jelovac 2014). The selection of basket countries is usually based on three main criteria: i) the geographic proximity of the reference countries, ii) comparable GDP and income levels and iii) similar socioeconomic conditions. Ex-factory prices are most frequently used in order to inform pricing decisions and regulators mainly rely on list prices rather than actual transaction prices to do so (Espin et al. 2014, Toumi et al. 2014, Leopold et al. 2012, Europe Economics 2013, Rémuzat et al. 2015 and European Commission 2015).

The method used to calculate the reference price usually differs across countries; often, the lowest in the basket is used but it is also common to use the average. The number of countries considered in the basket as well as the frequency of price revisions also varies across countries. In addition, the way ERP is implemented in a specific setting ultimately affects the impact it has within and across a country's borders. For example, if transaction prices were transparent and available for use in the ERP formula, and if more price revisions take place, then the implemented ERP system will be able to contain pharmaceutical costs and further lower the prices of pharmaceuticals within a country (Marinoso et al. 2011, European Commission 2014, Espin et al. 2014 and Houy and Jelovac 2014).

Overall, ERP is considered to be a straightforward and administratively simple system, as in theory most of the information is provided through publicly available sources or through an application submitted by manufacturers. However, ERP systems vary substantially in the way that they are implemented in different geographies, making them administratively complex and information- and resource-intensive in practice. As a result, the impact of ERP is difficult to study compared to other pricing approaches for pharmaceuticals.

ERP has been criticised over time, as numerous shortcomings have been identified with its use in different settings, including, among others, its perception as a price reduction and cost containment measure rather than an efficient resource allocation tool (Toumi et al. 2014, Leopold et al. 2012, OECD 2008, Kanavos et al. 2010, Aaserud et al. 2009). In addition, it is likely that ERP may lead to cross-country spillover effects such as pharmaceutical launch delays (European Commission 2009, OECD 2008, Europe Economics 2013, Danzon et al. 2005, Kanavos et al. 2010 and Espin and Rovira 2007). Price convergence, towards the basket's average, or lowest, price is observed as a result of ERP, while price instability can also be triggered as price fluctuations in one country generate greater price fluctuations in another (Leopold et al. 2012, Kalo et al. 2015, OECD 2008 and Toumi et al. 2014)

Although evidence exists on the different features of ERP systems, there is a lack of comparative analysis of empirical studies with clear methodological design and scarce evidence on the reasons why ERP impact varies across countries. In light of the above, this paper aims to fill this gap by studying the potential of ERP as a mechanism of pharmaceutical price regulation within and across countries over the short- and the longer-term in a systematic way by bridging the gap between concepts, practice and impact. Specifically, the paper objective is twofold: first, to gain a clearer understanding of the impact of ERP systems on important health system goals such as availability, affordability and diffusion/utilisation of pharmaceuticals; and, second, to study the impact ERP systems have at both a domestic and international level, particularly considering their likely spillover effects.

2. METHODS

In order to fulfil the above objectives, we conducted a systematic literature review that conforms to the guidelines for systematic reviews of the Centre for Reviews and Dissemination (CRD) (Centre for Reviews and Dissemination 2009).

2.1 STUDY ENDPOINTS

We divided the study endpoints into two groups, those addressing the impact of ERP within a country's own borders and those addressing the impact of ERP across countries (Table 1). At the country level, the relevant endpoints were selected in order to study how ERP affects the system-wide government policy objectives of a healthcare system, for example, the ability of ERP to secure "reasonable" prices (Leopold et al. 2012, Kanavos et al. 2010 and Toumi et al. 2014), the availability of pharmaceuticals in the country implementing ERP (Europe Economics 2013, Rémuzat et al. 2015 and Leopold et al. 2012), the affordability of ERP-controlled pharmaceuticals for a country's system and population (Lu et al, 2015 and Europe Economics 2013), the drug use changes as a result of ERP, the promotion of industrial policy (Kanavos et al. 2010) and the ability of ERP to contain pharmaceutical costs. The international impact of ERP was studied by considering the impact of ERP

on price stability and whether price fluctuations in one country cause greater price fluctuations in other countries (Leopold et al. 2012 and OECD 2008), the extent of price convergence across countries (Leopold et al.2012) and launch delays in third countries (Danzon et al. 2005 and Europe Economics 2013).

Further, within each endpoint, we identified key issues that every particular endpoint addressed. For instance, within the endpoint of cost-containment, we identified the following issues: (i) the ability of ERP to generate healthcare savings, (ii) the impact of the ERP design on cost-containment and (iii) whether ERP can lead to healthcare savings either in the short- or in the long-term.

2.2 DATA SOURCES, SEARCH STRATEGY AND KEYWORDS

To reduce the possibility of publication bias and ensure the identification of all relevant information, both peer-reviewed and grey literature was examined and included. Several databases were searched, as key information was likely to be found in both economics and policy-based literature; these were: the Web of Science (WoS), CINAHL, EconLit, Medline, ProQuest, the Cochrane Library and Scopus.

Table 1: Definition of Endpoints

Endpoints	Definition
I. Impact within countries	
Cost-Containment	The extent to which ERP has the capacity to reduce pharmaceutical spend.
Price Levels	Assesses whether ERP leads to or is able to secure reasonable prices for payers and healthcare systems.
Drug Use	Assesses whether ERP can manage excessive drug consumption
Availability	The extent to which new pharmaceuticals are available in the market for which they are intended.
Affordability	The extent to which pharmaceutical prices are congruent with the purchasing ability of health care systems and/or patients.
Equity	The ability of ERP to promote equitable access to medicines.
Efficiency	The extent to which ERP promotes health system efficiency and leads to optimal resource allocation.
Industrial Policy	Assesses whether ERP promotes and/or is consistent with the objectives of industrial policy (attracting manufacturing, R&D and/or related activities) or it acts as a barrier to attracting these.
II. Impact across countries or regions (spillover effects)	
Price Stability	Assesses the potential of ERP to help stabilize pharmaceutical prices so that random fluctuations caused by, among others, unrelated events such as currency fluctuations, are prevented.
Price Convergence	Examines whether ERP leads to price convergence (and whether this is upward or downward) or price divergence.
Launch Delays	Examines whether there are delays in the launch of new pharmaceuticals in third countries.

A combination of general and policy-specific keywords was used to ensure that relevant literature would be captured. All synonyms and different phrasings of External Reference Pricing were included in the search (see Appendix 1). The search run was: (“Pharmaceutical Price Regulation” OR “Pharmaceutical Regulation” OR “Cost Containment” OR “Pharmaceutical Pricing” OR “External Reference Pricing” OR “External Price Referencing” OR “International Price Comparisons” OR “International Reference Pricing” OR “International Price Referencing”) AND (drug OR drugs OR medicine OR medicines OR pharmaceutical OR pharmaceuticals).

Where possible, the search was restricted to keywords present within the abstracts only, to limit the number of irrelevant papers appearing in the search. When searching the WoS, the search terms were restricted to title only, as the option to restrict to abstract was not available.

In addition to the systematic literature review, targeted search of the WHO, the WHO collaborating centre for Pharmaceutical Pricing and Reimbursement Policies Gesundheit Österreich GmbH (WHOC- GOEG) and the OECD online databases was carried out to ensure that no relevant reports were omitted. The key words used to search these were “External Reference Pricing” OR “External Price Referencing” OR “International Reference Pricing” OR “International Price Referencing” (see Appendix I). Relevant information was recorded and combined with the results of the systematic literature review. Finally, additional literature gathered from contacts and wider internet searches was also included.

Language was restricted to English. There were no country-specific restrictions imposed on our search to ensure that evidence from as wide a geographical range as possible was collected. Our study included literature published from January 2000 to December 2016.

2.3 STUDY SELECTION, DATA EXTRACTION, EVALUATION AND SYNTHESIS

The systematic search went through different stages following the CRD guidelines. First, search results were filtered based on the relevance of the title and abstract to the topic. Papers with relevant titles were downloaded for further examination. The main body of these texts was then assessed for relevance against the inclusion criterion: ‘mention of external price referencing and impact’ at least on one of the selected endpoints: cost-containment, price levels, availability, affordability, launch delays, price convergence etc., in order to give a final set of relevant papers. The number of documents presenting evidence on each endpoint was noted. In situations where one study presented evidence on more than one endpoint, this was recorded separately each time.

An excel spreadsheet was used to extract the relevant information on each endpoint from the final set of papers included in the study. The spreadsheet comprised titles of the papers in the rows versus the endpoints in the columns, with important information from the texts being extracted and entered into the appropriate cell. A subsequent synthesis of the literature evidence was carried out to identify key trends and relationships regarding the impact of ERP policies in different countries or geographical regions.

In cases where the search yielded studies which were the product of a systematic literature review, they could only be included in our search if the endpoints considered were different from the ones set out in our analysis, in order to avoid possible bias.

As impact assessment studies in pharmaceutical policy have been found to be weak, often casting doubt on many of the conclusions (Kanavos et al. 2004), we critically assessed the quality and the strength of evidence used in this systematic literature review, by appraising the methodological design of the studies. We therefore categorized the studies into two groups: empirical and non- empirical studies. In the former category, randomized and non-randomized controlled trials, studies using quasi-experimental designs such as interrupted time-series and difference-in-difference analyses, other quantitative analyses such as before-after and post-only design were

considered. In the non-empirical category, theoretical models, descriptive studies as well as other literature reviews were considered. In those cases where descriptive studies provided quantitative evidence for a particular study endpoint(s), the initial piece of evidence was benchmarked against each endpoint and the quality of evidence was further examined as a part of the empirical evidence. Studies with strong quasi-experimental designs (i.e. time-series with a comparison group) and randomized controlled trials (RCTs), are considered to be well-controlled compared to before-after or post-only studies, which are considered to be partially controlled with weak research designs, often producing unreliable assessments of the impact of a pharmaceutical regulation (Kanavos et al. 2004). Therefore, the design of the empirical studies was examined in order to appraise the validity and reliability of our findings.

In order to assess whether we could have robust conclusions from the findings of this systematic literature review, we recorded whether the studies identified for each endpoint examined the short-term impact of ERP or its long-term impact against the selected endpoints. For example, if a study researched the possible price effects of ERP within a country in a limited time horizon of less than five years, then the extracted evidence would be short-term in nature and no major conclusions could be drawn on whether ERP has the ability to increase or decrease pharmaceutical prices. The studies that examined the impact of ERP against each endpoint with a study period of more than five years were considered to provide evidence over the long-term, allowing us to draw robust conclusions.

3. RESULTS

3.1 RESULTS OF LITERATURE REVIEW

The database search yielded 6,875 studies. The results of the systematic literature search were then combined with the results from the targeted search of the WHO, the WHO collaborating centre for pharmaceutical Pricing and Reimbursement policies (WHO CC) and the OECD online databases. Additional literature gathered from contacts was also included. By removing the duplicates using the EndNote software, 3,977 studies were initially screened based on relevant titles and abstracts. From the 3,977 studies, 3,489 were peer-reviewed papers and 488 were grey literature. Out of the 3,977 studies 3,430 records were excluded due to irrelevance of title or abstract. Therefore, 547 papers were then downloaded and assessed for eligibility. Studies were excluded for either non-relevance to ERP or when internal reference pricing was studied or at times when only the abstracts of those papers were available. The main body of 281 texts was then assessed for relevance against the inclusion impact criterion explained above. The detailed breakdown of the studies providing evidence on each of the endpoints included in this study can be seen in Table 2. There were 76 final papers/studies included in this systematic literature review, comprised of a significant proportion of grey literature (42 studies) and only 34 peer-reviewed papers (Figure 1).

Ten papers included in this systematic literature review were empirical studies, comprising about 13% of the total studies considered. Although the majority of the studies generated were descriptive papers, theoretical models or literature reviews, it has been observed that when examining the impact of ERP against the included endpoints, these papers used data collected by studies using a post-only design in order to capture the impact of ERP quantitatively. Under these circumstances, the original source of the data was studied and recorded.

One systematic literature review (Rémuzat et al. 2015) was extracted via our systematic literature search. The systematic literature review of Rémuzat et al. 2015, provided an overview of ERP systems in Europe both on processes and potential issues in all European countries including Iceland, Norway, and Switzerland. In this paper, the authors examined the use of ERP and its impacts on the prices of pharmaceuticals as well as the possible cross-

country coordination issues in European countries. The included endpoints were the following: (i) ERP processes in Europe; (ii) National legal framework; (iii) Scope of ERP; (iv) composition of the country basket; (v) price calculation and selection of reference products; (vi) limitations of ERP; (vii) potential consequences of ERP, including a) spillover effects and price convergence, b) patient access to medicines, c) affordability and d) industry revenue and sustainability. The scope and the endpoints studied in this systematic literature review differ from ours and our search strategy was not limited to specific countries. Therefore, we were able to include this paper in our analysis, which extends and supplements the work of Rémuzat and co-authors (see Appendix II). In addition other non-systematic reviews (Leopold et al. 2012 and Håkonsen et al. 2009), which differ in scope, were included in this systematic literature review.

Figure 1: PRISMA flow diagram outlining search results from the systematic literature review

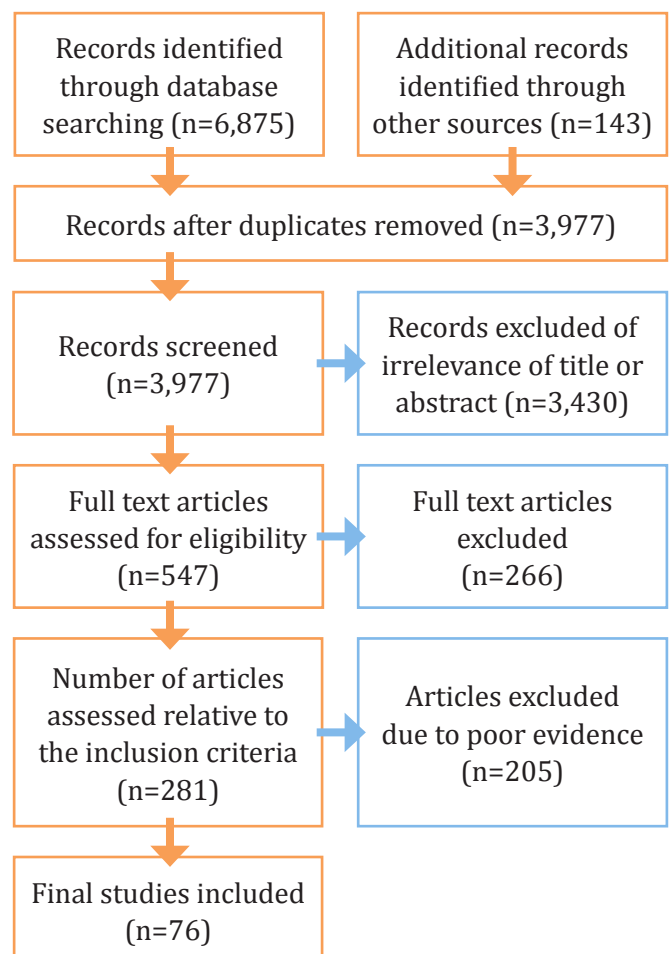


Table 2: Results of systematic literature search by source

	CINAHL	Cochrane Library	Econ-Lit	Pro-Quest	Pub-Med	Scopus	WoS	OECD	WHO	WHO-HiT	WHO-CC-PPRI	Network
No. of original studies	30	11	26	2,169	58	684	796	10	17	60	68	48
Peer-Reviewed studies	30	11	17	1,899	58	678	796	-	-	-	-	36
Grey Literature	-	-	9	270	-	6	-	10	17	60	68	12
No. of studies with relevant titles & abstracts	6	1	6	299	12	39	40	10	17	32	37	48
Peer-Reviewed studies	6	1	6	29	12	39	40	-	-	-	-	36
Grey Literature	-	-	-	270	-	-	-	10	17	32	37	12
No. of studies that match endpoints	2	0	1	104	5	15	10	10	17	32	37	48
Peer-Reviewed studies	2	-	-	11	4	15	10	-	-	-	-	36
Grey Literature	-	-	1	93	1	-	-	10	17	32	37	12
No. of studies that match ERP Impact endpoints	2	0	0	27	2	11	7	10	0	5	1	11
Peer-Reviewed studies	2	-	-	5	2	11	7	-	-	-	-	7
Grey Literature	-	-	-	22	-	-	-	10	0	5	1	4

3.2 IMPACT OF ERP WITHIN COUNTRIES

3.2.1 Cost-Containment

Seven studies provided evidence on whether ERP is used as a tool to contain pharmaceutical costs and the extent to which pharmaceutical savings can be obtained for governments. This endpoint reflects the fact that ERP is defined as a cost containment measure. Cost-containment incorporates both management of price levels and drug consumption. Of these seven studies, two were peer-reviewed and five were identified from grey literature. Five of the included studies were descriptive studies, describing the current situation in country level using data collected in a post-only design, either by the Ministry of Health and/or by other competent authorities (European Observatory, Health Systems in Transition – HiT: Turkey 2011, BMI Slovakia 2012; Yfantopoulos 2008: European Observatory, HiT: Greece 2010;

and OECD 2008), one designed a theoretical model to examine the influence of the ERP policy on the reference countries and the pharmaceutical firms (Marinosa et al. 2011), and, finally, one performed a literature review along with surveys and interviews, studying cross-country pharmaceutical pricing coordination. A simulation model was further built in the report to illustrate the general workings of ERP across Europe, in price setting and the impact that changes in ERP mechanisms may have on healthcare savings and on pharmaceutical prices (European Commission 2015). Three of the included studies considered the long-term effect of ERP as a cost-containment tool leading to healthcare savings over time (Yfantopoulos 2008, European Observatory, HiT: Greece 2010 and European Commission 2015).

The evidence collected on the performance of ERP as a cost-containment tool can be divided into three issues, which are discussed in greater detail below. The identified issues are (i) the ability of ERP to

generate healthcare savings, (ii) the impact of the ERP design on cost-containment and (iii) whether ERP can lead to healthcare savings either in the short- or in the long-term.

With regards to whether ERP is used as a successful cost-containment tool, it has been observed that “the conditions on the EU market are in effect weakening the use of cost-based price regulation and giving more importance to the observed price in other European countries using external reference pricing” (Marinoso et al. 2011). Across Europe, ERP has sometimes proven to be effective in generating substantial savings for public payers in the short-term, largely depending on the ERP methodology applied. Meanwhile, ERP impact on healthcare savings in the long-term is highly dependent on the pricing policies and the economic conditions existing within the country and across reference countries. In addition, the limited ability of ERP to serve as a cost-containment tool in the long-term can be partially attributed to the ‘fadeout’ effect (European Commission 2015).

Country-specific evidence on the performance of ERP as a cost-containment measure was identified. In Slovakia, in 2012 the new reference system was expected to create savings estimated at €75 million by the end of the year due to price reductions expected by ERP. This reformed ERP system set the pharmaceutical prices according to the average of the two lowest prices in the EU, replacing the previous system, in which pharmaceuticals could not exceed the average price of the six lowest prices for pharmaceuticals in other EU countries (BMI Slovakia 2012). In Turkey in 2007, ERP resulted in annual savings in the public sector of up to US\$ 900 million and led to considerable reductions in the prices of medicines, saving the government about US\$ 1 billion (European Observatory, HiT: Turkey 2011). Contrary to Turkey, when ERP was implemented in Greece in 1996, it initially led to a reduction in public spending. However, ERP proved to be ineffective in the long run as pharmaceutical expenditure continued to rise at similar rates to those before its introduction. This observation can be attributed to the replacement of older products by new, but not necessarily more effective, products within the same therapeutic category that were more expensive and more widely

prescribed by physicians. It has been concluded that at least in Greece, emphasis on price controls only is not effective in containing pharmaceutical expenditure because it is not accompanied by any policy interventions to control demand and volume consumption (Yfantopoulos 2008; European Observatory, HiT: Greece 2010).

While savings are likely to occur for publicly funded health care systems, the extent of such savings depends largely on the way that ERP is implemented. In Switzerland in 2010 and 2011, the government initiated a series of policy measures in order to contain the growth of pharmaceutical expenditure (European Observatory, HiT: Switzerland 2015). Changes in the implementation of the ERP system were made in order to put downward pressure on prices. For example, an increase in the number of basket countries used as reference and more frequent price revisions were initiated (OECD 2008). In several scenario-testing exercises by the European Commission 2015, two options were recommended in order to help public payers to generate more healthcare savings over time by decreasing pharmaceutical prices. In the first simulation exercise, an additional discount or rebate of 20% was applied to the prices of pharmaceuticals in large markets, based on high GDP, such as Germany, France, the UK, Italy, Spain, the Netherlands and Switzerland. In this report, it was argued that savings in countries implementing ERP could have been higher by 27%, if actual paid prices/discounted prices tended to be transparent and could be considered under ERP (European Commission 2015). In the second simulation exercise with more frequent price re-evaluations taking place, the European Commission 2015 reported that healthcare savings could also be higher in the long run, if more frequent price reviews with subsequent price revisions were performed by countries implementing ERP. In this scenario, they tested the extent of the price reduction if all countries re-evaluated their prices every six months. This resulted in a decrease of about 6% on the average price of all 28 European Countries. However, the administrative burden of conducting such re-evaluations should be balanced, where for instance frequent price revisions could be performed in medicines with high- budget impact or to a very small country basket (European Commission 2015).

Table 3: ERP and association with cost containment: Summary of the available evidence

Issues	Overall Evidence	Studies	Countries with evidence	Quantifiable Impact
Cost-Containment				
Healthcare Savings	European countries are introducing ERP to contain costs and increase healthcare savings. The evidence on the impact of introducing ERP in savings across countries varies.	<ul style="list-style-type: none"> • Marinoso et al. 2011 • BMI Slovakia 2012 • European Commission 2015 • European Observatory, HiT: Greece, 2010 • OECD 2008 • Yfantopoulos 2008 	<ul style="list-style-type: none"> • Slovakia • Turkey • Greece 	<ul style="list-style-type: none"> • Eur €75m (Slovakia, 2012) • US\$900m-US\$1bn (Turkey, 2007)
Healthcare savings depend on ERP Design	The extent of healthcare savings depends largely on the way ERP is implemented. Frequent price revisions and consideration of transaction prices could result in higher sustained savings.	<ul style="list-style-type: none"> • European Commission 2015 • OECD 2008 • Yfantopoulos 2008 • European Observatory, HiT: Switzerland, 2015 	<ul style="list-style-type: none"> • All EU countries and Switzerland 	<ul style="list-style-type: none"> • 'Consideration of actual discounted prices' • 'Frequent price revisions'
Short-term Vs. Long-term effect	Four studies provided evidence on the long-term effect of ERP on generating healthcare savings. At least in the short-term, ERP can be used as a tool to control costs, whereas in the long-term its impact on cost-savings is uncertain	<ul style="list-style-type: none"> • European Commission 2015 • European Observatory, HiT: Greece, 2010 • Yfantopoulos 2008 	<ul style="list-style-type: none"> • All EU countries 	<ul style="list-style-type: none"> • 'Only Short-term' (European countries, Slovakia, Turkey, Greece)

3.2.2 Price Levels

Twenty-six studies, ten peer-reviewed and sixteen from the grey literature, provided evidence on the impact of ERP on pharmaceutical prices and whether ERP leads to or is able to secure lower prices within a country. Whilst some studies may focus specifically on certain pharmaceutical products our analysis, aligned with government policy objectives, where the objective is generally to secure lower prices and ensure that prices are in-line with other countries, covers the average pharmaceutical prices within a country and is not concerned with prices of specific products. Of these twenty-six studies, eight were descriptive giving no quantitative evidence when discussing the potential impact of ERP on price levels. Eleven papers were descriptive in nature, either depicting the country situation at the time of the study or discussing how ERP is implemented in Europe, but complementary data from post-only analysis were used when the impact of ERP on the prices of pharmaceuticals products was discussed. The additional data used in these papers were either recorded by the Ministry of Health of the studied country, by other competent authorities or by key stakeholders (Kanavos et al. 2010, European

Observatory, HiT: Netherlands 2010, European Observatory, HiT: Republic of Moldova, 2012; the BMI reports). Two of the papers considered were empirical studies using regression models studying the effects of ERP (Leopold et al. 2012 and Danzon et al. 2005), while three papers performed simulation exercises (Merkur and Mossialos 2007, Toumi et al. 2014 and European Commission 2015) to test for circumstances under which prices of pharmaceuticals were affected by ERP. One included paper designed a theoretical model (Marinoso et al. 2011) and, finally, one performed a systematic literature review, looking into ERP systems across Europe and their potential consequences (Rémuzat et al. 2015). Out of the twenty-six studies considered for this endpoint, only nine studies considered or provided long-term evidence (i.e. a time period greater than 5 years), on the impact of ERP on price levels (Kanavos et al. 2010, Håkonsen 2009, Rémuzat et al. 2015, Toumi et al. 2014, Danzon et al. 2005, European Commission 2015, Espin et al. 2014, OECD 2008, Europe Economics 2013).

The evidence on the impact of ERP on prices at country level was organized into four issues. First, we examined whether ERP leads to an increase or

decrease of pharmaceuticals prices across countries in both the short- and long-term. Second, we focused on whether ERP is a meaningful regulation for setting lower pharmaceutical prices. Third, we explored the features of ERP that can potentially influence prices of pharmaceuticals in a country either upwards or downwards. Finally, we analysed how the features of the markets implementing ERP can further influence the price levels of pharmaceuticals.

Despite economic evidence on the impact of ERP on pharmaceutical prices being scarce, available literature generally shows that the introduction of ERP has reduced the price of pharmaceuticals in a number of European countries (Leopold et al. 2012, Koh et al. 2016, Marinoso et al. 2011 and Kanavos et al. 2010). Indeed, ERP implementation in the Netherlands resulted in considerably lower prices in general, while the average prices of Prescription Only Medicines (POMs) dropped dramatically by 8% between 2007 and 2008 (European Observatory, HiT: Netherlands 2010). In a simulation exercise testing possible effects of ERP introduction on drug prices in Cyprus, ERP seemed to lead to the reduction of prices, after identifying Cyprus as a high-price country for pharmaceuticals (Merkur and Mossialos 2007). In Norway, ERP was introduced in 2000 and since 2009, it has been regarded as very successful, resulting in considerable and predictable price reductions (Håkonsen 2009). In Moldova, the reform of ERP in 2010 decreased prices by 3% in 2011, reversing the previous upward trend in prices. In 2010, the government of the Republic of Moldova introduced a regulation on the Approval and Registration of Producers' Prices for Medicines in order to tackle the increase of pharmaceutical prices from 2006 until 2010. Under this regulation, the manufacturer's price is set based on the average price of the three lowest prices in the basket (European Observatory, HiT: Moldova 2012). In 2014 prices of POMs in Romania were found to be at a low level compared to the EU average statutory prices due to the use of ERP (Global Forum, OECD 2014). In Bulgaria in 2012 government changed the ERP design such that the basket was increased from eight to 12 countries and yearly price checks were implemented for all reimbursable pharmaceuticals. Prices of reimbursed pharmaceuticals fell by between 4%

and 75.4 % as a result (BMI Bulgaria 2015 and 2016). In Greece changes to the reference price system from September 2010 resulted in lower pharmaceutical prices – Eurostat data revealed an average price decrease of 9.5% in 2010 compared to the prices attained from the temporary price cuts regulation in May 2010 (BMI Greece 2012).

Despite these reductions ERP has also been criticized for not having a noticeable impact on price levels (Kanavos et al. 2010) and has been further characterized as 'not optimal' for leading to appropriate and competitive price levels over time compared to a more competitive and dynamic pricing system that would enable products to demonstrate value in their national context. It has been argued that ERP discourages flexibility of pricing according to local market conditions and tends to reinforce narrow price ranges across markets (EFPIA 2014).

Evidence has shown that transaction prices are often difficult to find, thus countries do not usually adopt real prices, but instead virtual list prices which are systematically and substantially higher, leading regulators to pay higher prices than they intend to pay (Espin et al. 2014, Kanavos et al. 2010, OECD 2008 and Rémuzat et al. 2015). This is because confidentiality restrictions, rebates, discounts, clawbacks and in general any price negotiation between third party payers and companies are in the majority of cases invisible and cannot be considered under ERP. In this case, ERP can be distorted in a number of circumstances by national regulatory policies which introduce invisibility of net transaction price, limiting ERP effects in lowering pharmaceutical prices within countries by not taking into account the lower discounted prices when referencing other countries (Kanavos et al. 2010, Europe Economics 2013 and Leopold et al. 2012). In addition, countries using ERP may reference artificially high prices, resulting in list-price inflation, while in the long run this phenomenon will render ERP ineffective and irrelevant as discounting and rebating are widely applied in pharmaceutical prices (OECD 2008 and Espin et al. 2014). On the other hand, it has been argued that only official list prices should be taken into account under ERP, in order to not undermine the flexibility of customers to agree to terms with the pharmaceutical manufacturer who often include multiple parameters (EFPIA 2014).

The price levels within a country are influenced predominantly by the nature and the rules of the implemented ERP system itself, such as the selected countries in the basket, the price considered in the basket and the frequency of price revisions. Other aspects of the market can influence the impact that ERP has on price levels, such as the country income level, the health needs of the population and the healthcare cost. Overall, ERP is characterised by a 'path dependence', in the sense that the information used for the system in terms of countries and prices most likely influences, to a certain degree, the final outcome (Leopold et al. 2012 and Rémuzat et al. 2015).

In terms of the relationship between price levels and the ERP design of each country, literature states that the most influential parameters on the evolution of the drug price over time, when ERP is implemented, are the frequency of price revisions, the size of the country basket and the ERP formula used. In various simulation exercises analysing the reaction of pharmaceutical prices with different ERP modalities, ERP systems lowered the prices of pharmaceuticals when frequent price revisions and iterative price cuts were applied, when country baskets were very large and when a country used the lowest price or average of the three lowest prices in the country basket rather than the average price when calculating reference prices (Toumi et al. 2014). Furthermore, countries with no price revisions over time tend to have flat prices. In the simulation exercises, countries with the smallest price decreases were Austria, Belgium, Cyprus, Denmark, Estonia, Germany, Iceland, Luxembourg, and Poland. The largest decreases were observed in Greece, Latvia, Lithuania and Slovakia (Toumi et al. 2014).

The Croatian ERP system was modified in 2012 when France was removed from the reference basket and replaced with Czech Republic, which was previously used as a backup reference country. This change in the basket had the added effect of reducing the price of most pharmaceuticals, as prices in the Czech Republic are generally lower than those in France (BMI Croatia 2013). In addition, it was observed that in Slovakia ERP tended to result in higher prices relative to neighbouring countries with similar income levels due to the basket country selection. This

is because the German price and the price of the originator country of the pharmaceutical are used to calculate the reference price; Germany tends to have relatively high ex-manufacturer prices and the country of manufacturer tends to be a high-priced country, given the production costs. However, in Slovakia, in 2009, ERP led to lower prices due to the ERP policy change which led to the calculation of the reference price using the mean of the six lowest countries within Europe (Kalo et al. 2008, Leopold et al. 2012). In Switzerland, in 2010, because of the increase in the number of reference countries in the basket, there was a higher possibility of further price reductions of pharmaceuticals (BMI Switzerland 2010, 2011 and 2012). Kanavos et al. 2010 analysed the effect of ERP on price in seven European countries for 11 pharmaceutical products between January 2003 and December 2008. Price reductions were observed in four of the seven countries. These countries calculated the reference prices using the average of the *n* lowest of the basket, or the lowest available price in the basket (Kanavos et al. 2010).

With regards to the variability of price levels due to the individual market features, Leopold et al. 2012, using a regression model adjusted on other exogenous factors that may affect price levels such as sales volume, exchange rates, gross domestic product (GDP), total pharmaceutical expenditure, and size of the pharmaceutical industry, concluded that prices are generally lower when a country applies ERP, even if substantial price differences among countries are observed. Countries with a high GDP per capita such as Norway, the Netherlands, Finland, Austria and Belgium have higher prices in the studied pharmaceuticals than countries with a lower GDP per capita such as Spain, Greece and Portugal. In the Netherlands, the price level of all the different pharmaceuticals studied was around the average (Leopold et al. 2012). Furthermore, Danzon et al. (2005) using a regression model, also estimated that countries with strict price regulation experience lower prices than less regulated markets (Danzon et al. 2005). Finally, in Lithuania in 2012, although prices of pharmaceuticals were already relatively low due to ERP, further downward pressures on prices were expected in light of fiscal concerns in the country (BMI Lithuania 2012).

Table 4: ERP and association with pharmaceutical prices: Summary of the available evidence

Issues	Overall Evidence	Studies	Countries with evidence	Quantifiable Impact
Prices				
Pharmaceutical Prices	Overall, the evidence has shown that pharmaceutical prices tend to decrease when ERP is implemented in most European countries and China.	<ul style="list-style-type: none"> • Leopold et al. 2012 • Håkonsen et al. 2009 • Koh et al. 2016 • Marinoso et al. 2011 • Merkur and Mossialos 2007 • BMI Bulgaria 2015 • BMI Greece 2012 • European Observatory, HiT: the Netherlands, 2010 • European Observatory, HiT: Greece, 2010 • European Observatory, HiT: Republic of Moldova, 2011 	<ul style="list-style-type: none"> • The Netherlands • Cyprus • Norway • Romania • Bulgaria • Greece • Slovakia • Republic of Moldova • China 	<ul style="list-style-type: none"> • 8% decrease of POM prices (the Netherlands, between 2007 and 2008). • Pharmaceutical prices decreased by 3% (Moldova, 2012) • Prices of reimbursed pharmaceuticals decreased between 4% and 75.4 % (Bulgaria, 2014) • Medicine prices decreased by an average of 9.5% (Greece, 2010)
ERP as a meaningful regulation to lower pharmaceutical prices both at launch and over time	Evidence in the literature has shown that ERP reference prices which are only related to list prices, rather than actual transaction prices, lead to higher pharmaceutical prices and limit the opportunities for countries implementing ERP to benefit from the actual lower prices attained in individual countries	<ul style="list-style-type: none"> • Leopold et al. 2012 • Kanavos et al. 2010 • Toumi et al. 2014 • Rémuzat et al. 2015 • EFPIA 2014 • OECD 2008 • Espin et al. 2014 • Europe Economics 2013 • European Commission 2015 	<ul style="list-style-type: none"> • All EU countries and OECD countries 	<ul style="list-style-type: none"> • No
Pharmaceutical prices depend on ERP Design	The extent of the reduction of pharmaceutical prices depends largely on the design of the implemented ERP. Frequent price revisions, larger basket of countries, wiser basket country selection and the consideration of the average or the lowest prices in the basket when calculating the reference price can lead to even more downward pressure in price levels.	<ul style="list-style-type: none"> • Leopold et al. 2012 • Rémuzat et al. 2015 • BMI Croatia 2013 • BMI Switzerland 2010 • BMI Switzerland 2011 • BMI Switzerland 2012 • BMI Bulgaria 2015 • BMI Bulgaria 2016 • European Observatory, HiT: Moldova, 2012 • Kanavos et al. 2010 • Toumi, M. 2014 	<ul style="list-style-type: none"> • Croatia • Austria • Belgium • Cyprus • Denmark • Estonia • Germany • Iceland • Luxembourg • Poland • Greece • Latvia • Lithuania • Slovakia • Switzerland • Moldova 	<ul style="list-style-type: none"> • 'Larger basket' • 'Basket country selection' • 'Frequent price revisions' • 'Calculation of reference price based on average or the lowest prices in the basket'

Continued

Table 4 continued: ERP and association with pharmaceutical prices: Summary of the available evidence

Issues	Overall Evidence	Studies	Countries with evidence	Quantifiable Impact
Prices				
Pharmaceutical prices depend on market features	Pharmaceutical prices correlate with country GDP per capita and can be affected by levels of market regulation, including ERP, and any economic pressure applied in the studied country	<ul style="list-style-type: none"> • Danzon et al. 2005 • Leopold et al. 2012 • BMI Lithuania 2012 	<ul style="list-style-type: none"> • Norway • The Netherlands • Finland • Austria • Belgium • Spain • Greece • Portugal • Lithuania 	<ul style="list-style-type: none"> • ‘Lower GDP levels’ • ‘Strict Price regulations’ • ‘Other fiscal concerns’
Short-term Vs. Long-term effect	A limited number of studies (35%, n=26) consider long-term evidence (study period over five years) when studying the impact of ERP on pharmaceutical prices. Therefore, whether ERP can or cannot continue to reduce prices over time is still unclear.	<ul style="list-style-type: none"> • Kanavos et al. 2010 • Toumi et al. 2014 • Rémuzat et al. 2015 • Danzon et al. 2005 • OECD 2008 • Espin et al. 2014 • Europe Economics 2013 • European Commission 2015 • Håkonsen et al. 2009 • Leopold et al. 2012 	<ul style="list-style-type: none"> • All EU countries and OECD countries 	<ul style="list-style-type: none"> • In the short and the long-term (Leopold et al. 2012 and Danzon et al. 2005 respectively)

It is questionable whether ERP actually provides a meaningful regulation aiming towards lower prices in pharmaceuticals, in a sense that the prices subject to ERP are prices only related to list prices, rather than actual transaction prices. In a simulation exercise examining the impact of ERP on healthcare savings and on pharmaceutical prices testing several scenarios, the majority of European countries seemed to profit at country-level by discounts, rebates or other special arrangements on the actual paid prices of pharmaceuticals, whereas the other referenced countries did not benefit from the actual lower prices implemented in individual countries (European Commission 2015).

3.2.3 Drug use

This endpoint measures the ability of ERP to control drug consumption within a country where the government objective centres around ensuring effective drug use. Evidence with regards to the impact of ERP on drug utilisation is scarce. Only one relevant source was identified, descriptive in nature, which reviewed Greece’s health system, reforms and policy initiatives in progress and concluded that at least in Greece, ERP failed to control medicines consumption as this is a factor which can be influenced by a variety of other determinants such as the number of prescribing doctors, the incentives driving their prescribing behaviour and patients’ demand (European Observatory, HiT Greece 2010).

Table 5. ERP and association with drug use within countries: Summary of the available evidence

Issues	Overall Evidence	Studies	Countries with evidence	Quantifiable Impact
Drug use				
Control consumption	ERP did not have an impact on medicines’ consumption as this is a factor largely influenced by a variety of other determinants such as the number of prescribing doctors or patients’ demand	<ul style="list-style-type: none"> • European Observatory, HiT: Greece, 2010 	<ul style="list-style-type: none"> • Greece 	<ul style="list-style-type: none"> • No
Short-term Vs. Long-term effect	There is no long-term evidence on whether ERP has an effect on drug consumption or whether ERP is a sufficient condition for the diffusion and use of pharmaceuticals	N/A	N/A	N/A

3.2.4 Availability

This endpoint measures the extent to which pharmaceuticals are available in the market. Government policy objectives focus on increased pharmaceutical availability in a timely manner with minimal access barriers. The issue of availability has attracted a great deal of interest in the study of ERP and its impact in different settings. As ERP takes into account the average or the lowest price of different reference countries it may result in a general price decrease when one country reduces its price and thus, if the price generated becomes too low, manufacturers have one of several options. For products already launched, they can proceed to market withdrawal of their product. Meanwhile, for new products awaiting launch, ERP can lead to launch delays, reduced volumes to accommodate high prices, or no launch, resulting in non-availability for these products (De Weerd et al. 2015; European Economics 2013).

Fourteen studies from EU countries were identified, which provided evidence on the impact of ERP on availability and accessibility of pharmaceuticals in a country. Eight of these studies were based on an empirical research design but they were all either pre-post or post-only studies without a comparator group. Of these eight studies, seven (European Commission 2015 2015; Vogler 2014; Toumi et al. 2014; Espin et al. 2014; Rémuzat et al. 2015; Kanavos et al. 2010; Håkonsen et al. 2009) analysed primary data from stakeholder consultations and surveys along with secondary data from the literature, either by proposing and testing a theoretical model (European Commission 2015 2015; Vogler 2014; Toumi et al. 2014), by conducting a mapping exercise (Espin et al. 2014), or by conducting a combined analysis (Rémuzat et al. 2015; Kanavos et al. 2010; Håkonsen et al. 2009), whereas one study (Vogler, Mantel et al. 2012) presented primary evidence on the impact of ERP on on-patent medicine prices based on a regression analysis model. Furthermore, six studies were descriptive, of which two comprised an ERP-specific, non-systematic literature review (Europe Economics 2013; Leopold, Vogler et al. 2012) and four provided some evidence on the impact of ERP in the context of reviewing the literature relevant to the impact of pharmaceutical and pricing policies on several health system goals in general (Atikeler

& Ozcelikay 2015; De Weerd et al. 2015; Kalo et al. 2008; Vogler et al. 2015). It was suggested that ERP may indirectly hinder the availability of medicines (Atikeler et al. 2015; Vogler et al. 2014; European Economics 2013).

Several sources have assumed that ERP might lead to product shortage in countries referencing the lowest price, due to discontinuations and parallel export (Espin et al. 2014; Rémuzat et al. 2015). In support of the above, a comparable study on the short and long-term effect of ERP in Europe found a discernible impact on availability in all seven EU countries included in the analysis, where manufacturers did not launch several products (a total of 11) in order to avoid expected low prices. Others have also specifically linked non-availability of medicines to the concept of “launch sequencing strategies” arising due to ERP, whereby companies delay or withhold drug launches in countries with highly controlled prices at ex-factory level or in countries with lower prices, especially if these are small markets referenced by countries with larger markets which are in turn used as references by others (Rémuzat et al. 2015; Leopold et al. 2012; Kalo et al. 2008; European Commission 2015; Toumi et al. 2014; Kanavos et al. 2010). Therefore, due to ERP policies, fewer drug launches and longer drug launch periods are most likely to take place in highly regulated and/or small markets than in markets with relative flexibility on pricing, or markets that are large in size, with higher GDP, increased public healthcare spending, a higher percentage of GDP on health expenditure and a higher price level of pharmaceuticals (Håkonsen et al. 2009; Espin et al. 2014). For example, one study showed that among 15 European countries, in Germany, where pricing is not regulated at ex-factory level, both prices and availability were the highest (Leopold, Mantel et al. 2012). Further evidence about launch sequencing strategies due to ERP comes from Belgium where companies systematically delayed dossier submission in order to avoid the Belgian price being included in other countries price-setting (i.e. typically not among the highest EU range) (Toumi et al. 2014). Other examples include Slovakia, where a change in its reference country basket to include all EU Member states resulted in companies disregarding the newly implemented prices or lobbying for exemptions of their products, leading to access delays (Leopold, Vogler et al. 2012). Similarly, in Bulgaria, around 200

Table 6. ERP and association with availability of medicines within a country: Summary of the available evidence

Issues	Overall Evidence	Studies	Countries with evidence	Quantifiable Impact
Availability				
Market withdrawal	ERP may result in a general price decrease when one country reduces its price, suggesting that, especially in Low Income Countries (LICs), if the price generated becomes too low, manufacturers may proceed to market withdrawal and subsequent unavailability of their product in these countries.	<ul style="list-style-type: none"> De Weerd 2015 Europe Economics 2013 Espin et al. 2014 Rémuzat et al. 2015 Kalo et al. 2008 	<ul style="list-style-type: none"> Bulgaria 	<ul style="list-style-type: none"> In Bulgaria about 200 products were withdrawn from the market in 2012
Launch delays, launch sequencing or no launch	Companies may delay, sequence or withhold drug launches in countries with highly controlled prices at ex-factory level or in countries with low price levels	<ul style="list-style-type: none"> Rémuzat et al. 2015 Leopold, Vogler et al. 2012 Kalo et al. 2008 European Commission 2015 Toumi et al. 2014 Espin et al. 2014 Leopold, Mantel et al. 2012 Kanavos et al. 2010 	<ul style="list-style-type: none"> Slovakia Germany Belgium EU countries 	<ul style="list-style-type: none"> Systematic delay of dossier submission by companies in order to avoid the Belgian price Some companies tried to ignore the process or actively lobby for exemptions for their products In Slovakia, after a change in its reference country basket to include all EU Member states Germany had the highest availability among 15 European countries. 11 products among 7 EU countries were not launched by manufacturers in order to avoid expected low prices
Short-term Vs. Long-term effect	Examples from the literature mainly showcase the short term impact of ERP on availability of medicines, although one example provided evidence about the long-term impact of ERP too. Both in the short and long-term, ERP has been found to have an impact towards availability of medicines.	<ul style="list-style-type: none"> Toumi et al. 2014 Rémuzat et al. 2015 Håkonsen et al. 2009 	<ul style="list-style-type: none"> EU countries 	<ul style="list-style-type: none"> Short-term <ul style="list-style-type: none"> In Bulgaria 200 products were withdrawn in 2012 Long-term <ul style="list-style-type: none"> -Within a 6 year period, 11 products among 7 EU countries were not launched by manufacturers in order to avoid expected low prices

products were withdrawn from the market in 2012 (Rémuzat et al. 2015; Toumi et al. 2014).

There is contradictory evidence on the impact of ERP in terms of availability. Whilst some studies show significant threats to the accessibility of medicines may be posed by ERP, particularly if any of the reference countries have strict pharmaceutical expenditure measures imposed due to the economic crisis (Vogler et al. 2015), others acknowledge that no conclusive empirical evidence exists to support claims of ERP-related non-availability of medicines (Espin et al. 2014; Kanavos et al. 2010).

3.2.5 Affordability

This endpoint examines the extent to which pharmaceutical prices are in line with the purchasing ability of healthcare systems or patients. A moderate body of the relative literature discussed the impact of ERP on medicines affordability. ERP policies typically inhibit manufacturers from offering lower prices to lower-income countries and therefore could potentially undermine affordability of medicines within a significant number of EU countries (European Commission 2015; European Economics 2013).

Ten studies provided evidence about the impact of ERP on medicines affordability. The relevant evidence was largely generated by descriptive studies, based on reviewing the ERP relevant literature (Europe Economics 2013), reviewing the literature on pharmaceutical policy and pricing strategies in general (Lu 2015) or providing a country specific pharmaceutical market research report (BMI Egypt 2010, 2011 and 2012). Only two empirical studies were found, which were both post-only studies that analysed primary data from stakeholder consultations and surveys, along with secondary data from the literature either by proposing and testing a theoretical (European Commission 2015) or a simulation (Toumi et al. 2014) model. Overall, three studies provided considerations about the access to and affordability of patented medicines in the EU, examining in particular the effects in LICs (Europe Economics 2013; Toumi et al. 2014; Lu 2015).

In Egypt it was found that whilst a decrease in price should alleviate public concerns around affordability,

the reference countries (which include Sweden, Austria, Finland and Switzerland) have higher per-capita spending figures than Egypt and therefore, even after a 10% mark-down, prices would still be relatively expensive for the local population (BMI Egypt 2010 and 2011). This could potentially trigger issues with affordability of medicines in some countries, both within and particularly outside the OECD, unless policy makers change pricing and reimbursement policies to adapt to the new market dynamics (Lu et al. 2015). For example, it has been suggested that if external reference prices are set based on some kind of affordability index whereby medicine prices are weighted by GDP with international comparisons made either at an average exchange rate i.e. for a year (Europe Economics 2013) or purchasing power parities (PPPs) (European Commission 2015; Europe Economics 2013), affordability and accessibility of medicines in lower income countries could be improved (European Commission 2015). Indeed, in Egypt reforms have been put on hold to

Table 7. ERP and association with affordability of medicines within a country: Summary of the available evidence

Issues	Overall Evidence	Studies	Countries with evidence	Quantifiable Impact
Affordability				
Affordability in High Income Countries	It has been noted that countries with high absolute price levels of pharmaceuticals, have relatively low price levels (pharmaceutical prices divided by GDP per capita)	<ul style="list-style-type: none"> Toumi et al. 2014 	<ul style="list-style-type: none"> Germany, Denmark, Ireland and Italy, 	<ul style="list-style-type: none"> Germany, Denmark, Ireland and Italy, have relatively low price levels (pharmaceutical prices divided by GDP per capita)
Affordability in LICs	ERP policies encourage higher pricing in LICs, directly undermining affordability of medicines in these countries	<ul style="list-style-type: none"> Europe Economics 2013 European Commission 2015 Toumi et al. 2014 Lu et al. 2015 BMI Egypt 2010 BMI Egypt 2011 	<ul style="list-style-type: none"> Poland, Romania Bulgaria Egypt 	<ul style="list-style-type: none"> Poland, Romania and Bulgaria, pay relatively more compared to their GDP per capita In Egypt, prices are relatively expensive for the local population
Scope for increasing affordability	If external reference prices are set based on some kind of affordability index which reflects national GDP either through an average exchange rate or PPPs affordability in LICs could be improved	<ul style="list-style-type: none"> Europe Economics 2013 European Commission 2015 Lu et al. 2015 	<ul style="list-style-type: none"> Egypt 	<ul style="list-style-type: none"> No
Short-term Vs. Long-term effect	There is no conclusive and/or empirical evidence that ERP undermines affordability over time	N/A	N/A	N/A

allow the authorities to consider a better alignment between Egypt and reference countries in terms of PPP, although the impact of the pricing reform will remain unknown until the authorities review the PPP in relation to the potential reference countries (BMI Egypt 2010, 2011 and 2012).

Moreover, to have affordable access to medicines, policy makers in lower-income countries may need to increasingly rely on confidential agreements to obtain lower effective prices through rebates or discounts, and thus discourage any external spillover impact of their list prices (Lu et al. 2015).

3.2.6 Equity

This endpoint examines the ability of ERP to achieve equitable access to medicines within a country. Six studies discussed the effects of ERP from the social equity perspective. Two of these studies presented primary data about the processes underlying the use of ERP (Espin et al. 2014) and the short- and long-term impact of ERP implementation (Kanavos et al. 2010). They both generated primary evidence from surveys with stakeholders, whereas the latter also comprised a descriptive component based on the ERP relevant literature. Four of these studies were descriptive, of which three were ERP specific and originated from the grey literature (EFPIA 2014; Europe Economics 2013; Global Forum on Competition-GFoC 2014), whereas one was from the peer-reviewed literature and studied ERP only in

the context of reviewing the pharmaceutical pricing environment of Russia (Rudisill et al. 2014).

It was demonstrated that ERP and parallel trade had an effect on social welfare by increasing prices in both higher- and lower-income countries, therefore undermining equitable and affordable patient access among EU citizens (EFPIA 2014), particularly for low-price, low-income countries (Global Forum on Competition-GFoC, 2014).

Considering the nature of data required to inform ERP implementation (e.g. country selection, available prices from across the country basket, revision dates), Kanavos et al. (2010) concluded that ERP might be primarily relying on pricing factors extrinsic to the health care system in which it operates. In support of that, Rudisill et al. (2014) also recognised that ERP policies do not address country specific health system priorities such as urgent price reductions when needed (Rudisill et al. 2014). Espin et al. (2014) provided several examples such as Belgium and Austria (with a 2012 GDP per capita of US\$37,883 and US\$ 42,408 respectively) referencing Romania (US\$12,802) and Bulgaria (US\$14,301) or Ukraine (US\$7,374) referencing Moldova (US\$3,415), and Pakistan (US\$2,880) referencing Bangladesh (US\$2,093), to argue that theoretically, such a structure would nurture inequalities among countries, as the difference in wealth between the referrer and the referenced country increases and the risk elevates in situations where the reference

Table 8. ERP and association with equity within a country: Summary of the available evidence

Issues	Overall Evidence	Studies	Countries with evidence	Quantifiable Impact
Equity				
Social welfare	ERP and parallel trade had an effect on social welfare by increasing prices in higher- and lower-income countries therefore undermining equitable and affordable patient access among EU citizens	<ul style="list-style-type: none"> • EFPIA 2014 • Global Forum on Competition (GFoC) 2014 	<ul style="list-style-type: none"> • EU countries 	<ul style="list-style-type: none"> • Levelling of prices signifying less affordable pharmaceutical products
Policy objectives	ERP might be primarily relying on pricing factors extrinsic to the health care system in which it operates and subsequently might neglect country specific health system priorities	<ul style="list-style-type: none"> • Europe Economics 2013 • Rudisill et al. 2014 • Kanavos et al. 2010 • Espin et al. 2014 	<ul style="list-style-type: none"> • No 	<ul style="list-style-type: none"> • No
Short-term Vs. Long-term effect	There is no evidence on whether ERP has an effect on social welfare only in the short-term or over time	N/A	N/A	N/A

price is defined as the lowest price in the basket (Espin et al. 2014).

Finally, in support of the above, a descriptive report debating whether or not ERP can harm the interests of EU patients suggested that the prices of the basket countries reflect the referenced countries' policy objectives, such as domestic political concerns or the health structure of the domestic population, which might not only be of little concern to the referrer country but may also be antithetical regarding the policy objectives pursued by the referrer country (Europe Economics 2013).

3.2.7 Efficiency

This endpoint examines the impact of ERP on the efficiency of the health system and its ability to lead to effective resource allocation. Evidence on the impact of ERP on efficiency was only identified in three sources, of which two were EU specific comparative analyses; one comprising a descriptive

analysis of ERP policy characteristics in 28 EU countries (Leopold, Vogler et al. 2012) and one being a combined analysis of primary data from stakeholder consultations and secondary data from the literature on ERP (Rémuzat et al. 2015). The third was a country-specific, descriptive, market research report, which examined aspects of the Swiss policy environment and market characteristics and assessed the degree to which Switzerland has achieved certain policy goals (Paris and Docteur 2007). The metrics of the impact of ERP on efficiency used in the above mentioned studies included the ability of ERP to (a) reduce prices, (b) contain the rate of increase in drug costs or (c) contain the percentage of drug spend as a proportion of total health spend.

A descriptive overview of national ERP systems in EU countries showcased that in terms of efficiency, ERP led to a 25% reduction in the proportion of pharmaceutical expenditure as a percentage of total health care spending in Slovakia in 2009, when the EURO was implemented as the country's legal tender.

Table 9. ERP and association with healthcare system efficiency within a country: Summary of the available evidence

Issues	Overall Evidence	Studies	Countries with evidence	Quantifiable Impact
Efficiency				
Affordable prices (through price revision)	ERP may potentially increase efficiency in terms of affordable prices, especially through frequent periodic price revisions of listed drugs.	• Leopold, Vogler et al. 2012	• Slovakia	• In Slovakia, ERP based on the arithmetic mean of the six lowest countries within EU 26 countries, resulted in a 25% reduction of pharmaceutical expenditure as proportion of total health care spending.
Stable share of drug spend as proportion of total health spend	ERP might have the ability to reduce the proportion of pharmaceutical expenditure as a percentage of total health care spending	• Leopold, Vogler et al. 2012	• Slovakia	• In Slovakia, ERP based on the arithmetic mean of the six lowest countries within EU 26 countries, resulted in a 25% reduction of pharmaceutical expenditure as proportion of total health care spending.
Containing costs while guaranteeing access to medicines	Evidence about the impact of ERP on efficiency in the context of cost-containment, while maximising accessibility is inconclusive.	• Rémuzat et al. 2015	• No	• No
Short-term Vs. Long-term effect	Examples from the literature highlighted the short term impact of ERP on efficient drug expenditure by lowering prices, although no conclusive evidence was found to assess whether the impact of ERP on social equity and welfare is short or long-term.	• Leopold, Vogler et al. 2012	• Slovakia	• In 2009 , in Slovakia, ERP resulted in 25% reduction in the proportion of pharmaceutical expenditure as proportion of total health care spending

This was accompanied by a change in its ERP policy, which included the introduction of ERP based on the arithmetic mean of the six lowest countries within EU 26 (Leopold, Volger et al. 2012). Furthermore, a case study in Switzerland demonstrated that reliance on external and internal price benchmarking, rather than pharmacoeconomic assessment, as a basis for establishing prices, might have scope to optimise a country's pharmaceutical expenditure (Paris and Docteur 2007). This study recognised the potential of ERP as a mechanism to enhance efficiency in drug expenditure, particularly through frequent periodic price revisions of listed drugs, although assessment of the impact of these revisions was not available. Finally, one source assessed the impact of ERP on efficiency in the context of leading to cost-containment while maximising accessibility, but highlighted inconclusive evidence (Rémuzat et al. 2015).

3.2.8 Industrial policy

This endpoint measures the extent to which ERP promotes and/or is consistent with the objectives of industrial policy.¹ Objectives centre around incentives for R&D investment, increased revenues for manufacturers, effective entry and penetration of generic drugs. Eight studies were identified that provided evidence on the impact of ERP on industrial policy and innovation within a country. Only half of the relevant sources originated from the peer-reviewed literature and all of these presented empirical evidence generated from analyses of surveys and consultations with stakeholders about the short- and long-term effect of ERP implementation (Kanavos et al. 2010), the application and potential issues of ERP in Europe (Rémuzat et al. 2015), the processes underlying the use of ERP (Espin et al., 2014) and the quality of existing evidence on the impact of pharmaceutical policy practices (Espin &

Rovira 2007). Further evidence was available in the grey literature, comprising mainly country-specific market research reports (BMI Slovakia 2010; BMI Germany 2015 and 2016) and one intergovernmental report, which presented evidence on ERP in the context of assessing how pharmaceutical pricing and reimbursement policies have contributed to the achievement of certain health policy objectives among the OECD countries (OECD 2008).

It has been argued that price convergence, generated by ERP-based systems, discourages incremental innovation from pharmaceutical companies by reducing revenues and resulting potential for research and development investment (Rémuzat et al. 2015). For example, in Slovakia in 2009 their new reference pricing system forced the prices of drugs down and had an impact on the revenues of pharmaceutical companies (BMI Slovakia 2010). Overall, the relevant sources noted that ERP is likely to have an impact on incentives for investment that is disproportionate to the size of the "early launch" and/or "frequently referenced" countries' markets (OECD 2008). Another source suggested that ERP might specifically limit the generic industry's potential to enter specific markets by driving down the prices to unsustainable levels (Rémuzat et al. 2015). More precisely, it highlighted that from the European Generic Medicines Associations (EGA) perspective, ERP hinders generic penetration in specific markets as it generates unsustainable levels of prices. For example, the price of the generic olanzapine dropped by up to 98% in Bulgaria due to application of ERP in Denmark, thus limiting patient access to this medicine in Bulgaria (Rémuzat et al. 2015).

Further discouragement of industry innovation could be generated in cases where countries use various determinants in their external reference price set up, but do not clearly explain whether and how these determinants are valued or combined, creating regulatory uncertainties which might ultimately discourage potential manufacturers from pursuing research and development investments (Espin et al. 2014). For example, relative to Portugal and Austria, ERP rules are poorly defined in Germany; under these broad rules, research based pharmaceutical firms will find themselves less able to profit from incremental innovation in drug discovery (BMI Germany 2015 and 2016).

1 According to the Pharmaceutical Forum Progress report published by the European Commission in 2007, cost-containment policies such as ERP can create sufficient headroom needed for rewarding valuable innovation. This could be achieved by providing affordable prices, being consistent when giving rewards and being transparent in the pricing and reimbursement decision process. In addition, exemptions can be applied under cost-containment mechanisms for innovative pharmaceuticals that are considered highly valuable (Pharmaceutical Forum Report 2007).

Despite the above observations, a study conducting interviews with stakeholders of government agencies implementing ERP revealed the potential of ERP to enable value assessments, and therefore promote industry innovation (Kanavos et al. 2010). It was suggested that even though encouragement and reward of innovation is not explicitly the objective of ERP itself as a policy tool, innovation may be rewarded in the context of defining the basket of comparators (i.e. inclusion of countries that explicitly recognize value and the “value of innovation”) or in

the context of adjusting prices frequently to reflect price adjustments in other settings, or even by implementing ERP as a ‘light’ option, for example, at launch only (Kanavos et al. 2010).

Finally, one source assessing the existing evidence on the impact of pharmaceutical policy practices in Europe concluded that there is no clear evidence due to the multiplicity of factors involved and the long causality chain linking non-regulated pricing to innovation (Espin & Rovira 2007).

Table 10. ERP and association with industrial policy and innovation within a country: Summary of the available evidence

Issues	Overall Evidence	Studies	Countries with evidence	Quantifiable Impact
Industrial policy & Innovation				
Innovation and investment in R&D	ERP may discourage incremental innovation and investment in R&D through: (a) downward price convergence potentially leading to reduced revenues for pharmaceutical companies, (b) encouragement of parallel trade potentially leading to manufacturers’ investing in producing only marginal product modifications in order to avert the threat of parallel trade and (d) relatively general – rather than precise – definition of ERP rules and determinants, which creates regulatory uncertainties that potentially discourage manufacturers from pursuing R&D investments	<ul style="list-style-type: none"> • Rémuzat et al. 2015 • Espin et al. 2014 • BMI Germany Q1 2015 • BMI Germany Q1 2016 	<ul style="list-style-type: none"> • Slovakia • Germany 	<ul style="list-style-type: none"> • Poorly defined ERP rules in Germany render firms less able to profit from incremental innovation in drug discovery
Generics’ entry and penetration	ERP might limit the generic industry’s potential to enter specific markets by driving down the prices to unsustainable levels	<ul style="list-style-type: none"> • Rémuzat et al. 2015 	<ul style="list-style-type: none"> • Bulgaria 	<ul style="list-style-type: none"> • The price of the generic medicine olanzapine that dropped by up to 98% in Bulgaria due to application of ERP in Denmark
ERP influences manufacturing and/or R&D investment decisions	There is no clear evidence about the impact of pharmaceutical policy practices on industrial decisions in Europe due to the multiplicity of factors involved and the long causality chain linking non-regulated pricing to innovation	<ul style="list-style-type: none"> • Espin & Rovira 2007 	<ul style="list-style-type: none"> • No 	<ul style="list-style-type: none"> • No
Scope for promoting innovation	ERP could indirectly incentivise innovation through favourable basket and other parameter definition. Innovation may be rewarded in the context of defining the basket of comparators (i.e. inclusion of countries that explicitly recognize value and the “value of innovation”) or in the context of adjusting prices frequently to reflect price adjustments in other settings	<ul style="list-style-type: none"> • Kanavos et al. 2010 	<ul style="list-style-type: none"> • EU Member States 	<ul style="list-style-type: none"> • No
Short-term Vs. Long-term effects	Very limited evidence suggests that ERP might in the short-term deter manufacturers from investing in R&D	<ul style="list-style-type: none"> • BMI Slovakia, 2010 	<ul style="list-style-type: none"> • Slovakia 	<ul style="list-style-type: none"> • In 2009, in Slovakia, the new reference pricing system forced the prices of drugs down and had an impact on the revenues of pharmaceutical companies

3.2 INTERNATIONAL IMPACT OF ERP

3.3.1 Impact across borders

In this section, we study the impact of ERP in a country across other countries referencing this country. In contrast to the previous section, where we studied the performance of ERP against the government policy objectives, this section concentrates on cross-border implications of ERP. These general ‘spillover’ effects are to be expected to a certain extent due to the nature of the policy; however, they can prove problematic for the achievement of national government policy objectives. Whilst in the following sections we analyse the evidence against specific cross-border phenomena that might be caused by ERP, such as price stability and price convergence, this section focuses on the general observations and trends caused by spillover effects.

Eleven studies described in general the type of cross-country spillover effects caused by ERP systems and how these might be triggered. Three of these studies were peer-reviewed and eight were extracted from the grey literature. Eight studies provided descriptive evidence drawn from Europe and on the current country specific situation (Kalo et al. 2008, Pudersell et al. 2007, Rudisill et al. 2014, European Commission 2015, OECD 2008, Lu 2015, BMI Italy 2009 and 2010), whereas two descriptive studies provided empirical evidence of a post-only design using data from IMS and from competent authorities, when studying potential spillover effects of ERP (Europe Economics 2013 and Rémuzat et al. 2015). The last study was an empirical study using a regression analysis model to examine the potential impact of ERP on pharmaceutical prices (Leopold et al. 2012).

Of the eleven studies identified, four studies provided long-term evidence on certain spillover effects such as price convergence caused by ERP across countries over time (European Commission 2015, Europe Economics 2013, Rémuzat et al. 2015 and OECD 2008).

Upon studying the impact of ERP across borders, three specific issues were identified: (a) the potential spillover effects caused across countries when ERP is implemented, (b) whether spillover effects are observed over time, and (c) possible reasons why these effects can be experienced at a larger extent.

In empirical studies of the potential spillover effects of ERP across countries, three potential

phenomena were primarily discussed. First, the wider implementation of ERP is often associated with higher prices in LICs, while in the absence of ERP policies across countries, lower prices may have been the result (European Commission 2015, OECD 2008, Lu 2015, Europe Economics 2013 and Leopold et al. 2012). In other words, when LICs implement ERP, they are likely to get a reference price calculated by a basket where countries with higher income and higher prices might have been included; at the same time, in LICs, where ERP is not in place or not used as an aid for price negotiations, the government can easily negotiate the price of pharmaceuticals with manufacturers due to local price competition. In 2007, Estonia used ERP as a part of their price agreements between the Ministry of Social Affairs and manufacturers. As Estonia used similar economic markets such as Latvia and Lithuania in the country basket manufacturers were forced to lower pharmaceutical prices (Pudersell et al. 2007). However, an example from Slovakia showed the potential spillover effects caused by ERP, whereby when the Ministry of Health allowed a launch price that is 10% higher than the average price of the three lowest-priced reference countries, pharmaceutical companies were generally able to price their drugs above the lowest price elsewhere in Europe, allowing room for some companies to launch their products in Slovakia before the price was established in other low price countries and to keep the Slovak price higher than elsewhere in Europe (Kalo et al. 2008).

Second, ERP systems may affect the price levels of pharmaceuticals. In cases where prices are reduced, manufacturers’ willingness to set prices according to ERP is minimized (Rudisill et al. 2014, European Commission 2015, OECD 2008 and Lu 2015, Europe Economics 2013 and Leopold et al. 2012).

It has been observed that ERP experienced in Europe can create spillover effects from low-price to higher-price countries, leading to patient access issues due to shortages in low-price markets and at the same time resulting in limited benefits to payers and patients in terms of cost-savings, for high-price markets (Europe Economics 2013 and Rémuzat et al. 2015).

Rémuzat et al. (2015) showcased the potential spillover impact of ERP across countries in the case of a price reduction due to ERP in a single country implementing ERP, referencing two quantitative studies of Charles River Associates 2013 and EFPIA

Table 11: ERP and its impact across borders: Summary of the available evidence

Issues	Overall Evidence	Studies	Countries with evidence	Quantifiable Impact
Impact Across Borders				
Spillover Effects	ERP implementation is associated with spillover effects that can be observed, across countries. These can cause higher prices in LICs, launch delays and encourage 'launch sequencing' strategies from pharmaceutical manufacturers	<ul style="list-style-type: none"> Rudisill et al. 2014 Pudersell et al. 2007 Kalo et al. 2008 European Commission 2015 OECD 2008 Lu 2015 Europe Economics 2013 Leopold et al. 2012 	<ul style="list-style-type: none"> All EU countries All OECD countries 	<ul style="list-style-type: none"> In Estonia, in 2007, manufacturers were forced to lower pharmaceutical prices due to the reference countries 10% price drop in Greece has estimated losses for the industry of €299 million in Greece, €799 million in Europe, and €2,154 million worldwide (2010) a 10% price reduction in the Swiss price would reduce industry revenue by €430 million in Switzerland and €495.2 million worldwide (2010)
Extent of spillover effects	External Reference Pricing observed in the European market can cause substantial spillover effects. In addition, potential price reductions in commonly referenced countries could lead to substantial monetary loss across countries	<ul style="list-style-type: none"> Europe Economics 2013 Rémuzat et al. 2015 BMI Italy 2009 BMI Italy 2010 	<ul style="list-style-type: none"> Greece Switzerland Italy 	<ul style="list-style-type: none"> 10% price drop in Greece has estimated losses for the industry of €299 million in Greece, €799 million in Europe, and €2,154 million worldwide (2010) a 10% price reduction in the Swiss price would reduce industry revenue by €430 million in Switzerland and €495.2 million worldwide (2010)
Short-term Vs. Long-term effect	Whether ERP causes spillover effects in the short-term or over time has not been studied extensively in the literature. However, evidence from Italy showed that the effects of price decreases across Europe are expected to cause further pharmaceutical price erosion in this country over time.	<ul style="list-style-type: none"> BMI Italy 2009 BMI Italy 2010 Rémuzat et al. 2015 European Commission 2015 OECD 2008 	<ul style="list-style-type: none"> Italy 	<ul style="list-style-type: none"> In Italy, price decreases will probably lead to price erosion over the coming years (2009 and 2010)

2015. In these two studies the industry costs following a 10% pharmaceutical price drop in both Greece and Switzerland in 2011 were estimated separately, assuming all countries re-referencing Greek/Swiss prices were included. A 10% price drop in Greece was accompanied by estimated losses for the industry of €299 million in Greece, €799 million in Europe, and €2,154 million worldwide, whereas a 10% price reduction in the Swiss price reduced industry revenue by €430 million in Switzerland and €495.2 million worldwide (Rémuzat et al., 2015).

In Italy, the effects of price decreases across Europe were found to cause price erosion in the entire pharmaceutical market (BMI Italy 2009 and 2010).

3.3.2 Price Stability

This endpoint considers the potential of ERP to help stabilise pharmaceutical prices across countries such that random fluctuations, for example due to the effect of different currencies, are prevented. Although this does not necessarily indicate that all countries

regardless of their income per capita should pay the same price for pharmaceuticals, but rather relates to comparable countries, which are stable. Seven studies presented evidence about the impact of ERP on price stability, including four peer-reviewed studies and three studies from the grey literature. Of these seven studies, two were descriptive, presenting different pharmaceutical pricing regulations as well as the modalities of ERP in European countries and its potential impact (Ruggeri and Nolte 2013; Lu 2015), and one study developed simulation models to test several hypothesis about ERP effects (Toumi et al. 2014). Empirical evidence was collected by one study using a regression model (Leopold et al. 2012) and by three descriptive studies looking into ERP systems across European and OECD countries, referencing other studies employing a regression analysis or a post-only design to examine whether ERP promotes price stability (OECD 2008, Kanavos et al. 2010 and Leopold et al. 2012). Three out of the seven studies provided evidence on the potential long-term effect of ERP on price stability (Toumi et al. 2014, Kanavos et al. 2010 and OECD 2008).

The evidence from this endpoint addresses four specific issues: (i) whether ERP has the ability to promote price stability across countries and if so how, (ii), whether price stability is realised in the short- medium- and long-term; as well as examining possible reasons that might affect the level of price stability, including (iii) the ERP methodology or (iv) other externalities.

Regarding ERP's ability to produce stable prices across countries, the literature has shown that the impact of ERP on the prices of other countries is not well understood. This is partly attributable to the substantial price differences among European countries implementing ERP (Leopold et al. 2012).

The various modalities in ERP designs across countries may affect price stability. Countries not only vary in the number of countries and the actual countries included in the reference basket but they also tend to employ different calculation methods to determine the reference price (Ruggeri and Nolte 2013). The trend, however, seems to be that lower-price countries are used as a reference, while the reference price is derived as a function of the lowest third or quartile in the selected basket. In addition, the use and frequency of price revisions, exchange rate volatility and the

tendency of country baskets to revert towards the lowest price, play a significant role in price stability. The aforementioned may exert a downward pressure on pharmaceutical prices in the mid- to long-term in a particular country and lead to cross-border knock-on effects (Kanavos et al. 2010). In particular, the frequency of price revision is an important driver of price changes over time when applying ERP. It has been estimated that for a systematic price revision every year, the price decrease almost doubled compared to when price revisions were taking place every three years (Toumi et al. 2014). Thus, revising the intensity of price revisions for all countries, will affect countries with long periodicity, as increasing the revision frequency will contribute to decreasing the overall pharmaceutical prices. This price decrease will have a further impact on the prices in countries with high frequency of revision because of the referencing system (Toumi et al. 2014). Other factors related to ERP design, such as differing approaches used to tackle exchange rate fluctuations within the basket, the size of the basket and the ERP formula used may also have an effect on price stability, however evidence on this in the literature is lacking.

With regards to other potential external factors that could affect price stability, ERP places greater pressure on countries that are referenced by others to keep prices high, when early market entry is preferred for new products or when ERP is used to support a national pharmaceutical industry. As a consequence, there is a tendency for pharmaceutical manufacturers to set high entry prices for new products in countries with no strict regulations, making these prices indicative for other countries that use ERP as a way to regulate prices on their markets (Leopold et al. 2012). For example, if manufacturers accept a low price in one country, it may not only undermine their future price in a third country where the product has not been launched yet, but may also undermine revenue based on its current higher price in the first country, due to parallel exports (OECD 2008).

It has also been argued that the impact of other countries prices on the launch prices in a given country varies according to the type of pharmaceutical product. Evidence from Europe shows that launch prices of innovative (and highly efficacious) products are positively correlated to the lowest price received in high-price countries but the launch prices of 'me too'

Table 12: ERP and price stability: Summary of the available evidence

Issues	Overall Evidence	Studies	Countries with evidence	Quantifiable Impact
Price Stability				
ERP ability to promote price stability across countries	Overall, the impact of ERP on prices of other countries is not very well understood. However, the ability of ERP to stabilize pharmaceutical prices depends largely on other market characteristics as well as on the ERP design.	<ul style="list-style-type: none"> Ruggeri and Nolte 2013 Leopold et al. 2012 	<ul style="list-style-type: none"> EU countries 	<ul style="list-style-type: none"> No
Price stability depends on ERP design	The extent to which price stability is succeeding across countries depends largely on the design of ERP. The intensity of price revisions, the composition of the countries in the basket and the number of reference countries can either promote or hinder price stability across borders.	<ul style="list-style-type: none"> Toumi et al. 2014 Kanavos et al. 2010 Ruggeri and Nolte 2013 	<ul style="list-style-type: none"> All EU Countries USA New Zealand Japan Australia Canada Mexico South Africa 	<ul style="list-style-type: none"> A systematic price revision every year almost doubled the price decrease compared to prices when revision occurs every three years
Price stability depends on market characteristics	Price stability depends on the countries used as reference and whether the implemented price regulation is strict, on the category of pharmaceuticals, which are subject to ERP and on other confidential rebates/clawbacks that are implemented in each reference country.	<ul style="list-style-type: none"> Leopold et al. 2012 Leopold et al. 2012 OECD 2008 Lu 2015 	<ul style="list-style-type: none"> All EU Countries 	<ul style="list-style-type: none"> €1 reduction in Germany would lead to a price reduction of €0.09 in Austria with additional reduction of €0.15-€0.19 due to an indirect effect
Short-term Vs. Long-term effect	Four of the studies that were included in this endpoint provided long term evidence on ERP's ability to promote price stability across countries. The frequency of price revisions and the exchange rate volatility play a significant role to price stability and might increase the prices of pharmaceuticals in the mid- to long-term.	<ul style="list-style-type: none"> Kanavos et al. 2010 Toumi et al. 2014 	<ul style="list-style-type: none"> All EU Countries USA New Zealand Japan Australia Canada Mexico South Africa 	<ul style="list-style-type: none"> No

products are positively correlated to the lowest price received in high-price EU countries only. Consequently, price changes in one country influence prices in other countries (OECD 2008 and Leopold et al. 2012). When assessing the impact of a €1 price reduction in Germany on the prices of drugs in some European countries using ERP (i.e. Austria, Greece, Ireland, Italy, Luxembourg, the Netherlands and Portugal) it was found that the €1 price reduction in Germany was translated to a price reduction of €0.09 in Austria (which uses Germany as a reference). Furthermore, there would be an additional reduction of €0.15 – €0.19 due to an indirect effect, as Austria benchmarks several countries that use Germany in the reference basket. Therefore, price

changes in Germany may have cross-border impacts in countries referencing Germany (Leopold et al. 2012). The practice of agreeing to confidential rebates can also have an external effect, as countries using ERP may reference non-transactional prices, resulting in list-price inflation. In addition, claw-backs have a similar impact as the price is effectively changed post-purchase, after the list price has already affected the global price through ERP (Lu 2015).

In conclusion, the fact that confidential list price discounts exist can damage the credibility of ERP, such that it acts purely as a starting point in price negotiations.

3.3.3 Price Convergence

This endpoint examines whether ERP leads to either upward or downward price convergence or price divergence across the countries using ERP. Twelve studies were identified that presented evidence about the impact of ERP on price convergence. Of these, seven were peer-reviewed and five were derived from the grey literature. Three of the twelve studies were descriptive, discussing the current healthcare situation of the study countries (BMI Switzerland 2010 and 2012 and BMI Germany 2011), two created a simulation exercise to assess the price dynamics through ERP-based systems (Espin et al. 2014 and Toumi et al. 2014) and one developed a theoretical model to study whether pharmaceutical firms are incentivised to launch their products in countries implementing ERP (Houy and Jelovac 2014). Empirical evidence was extracted from six studies, of which two used data through a post-only design, collected either from competent authorities or the Eurostat database (OECD 2008 and Rémuzat et al. 2015) and four studies analysed quantitatively whether ERP leads to price convergence using either regression analysis (Leopold et al. 2012, Kanavos and Vandoros 2011, Kalo et al. 2015) or difference-in-differences analysis (Leopold et al. 2013). Four out of the twelve studies provided long-term evidence by studying the effect of ERP on price convergence over a period of more than five years (Toumi et al. 2014, Leopold et al. 2013, Rémuzat et al. 2015 and OECD 2008).

One predictable impact of ERP when implemented across countries is some international price convergence/harmonisation, although evidence from the literature is contradictory (OECD 2008). Three issues were identified under this endpoint: first, the overall ability of ERP to harmonize prices across countries; second whether this ability is observed over the long-term; and third, the factors affecting the trend of price convergence, which can be upwards, downwards or towards the mean. The last subsection is divided into two issues describing how price convergence can be influenced by the methodology of ERP or by other exogenous factors.

Some price convergence has been detected in certain European countries, Canada and other OECD countries, due to the extensive use of ERP in these (OECD 2008, Kanavos and Vandoros 2011).

In the Middle East, evidence from 2014 suggested that ERP systems reduced the pharmaceutical price differentials between countries with different economic status, resulting in a narrower price corridor for innovative pharmaceuticals, when the average and minimum prices of each pharmaceutical group were compared to the average of mean prices of Middle Eastern countries. Innovative pharmaceuticals resulted in a price corridor of -39.8% and +35.9% of the average of the mean prices in study countries compared to non-pharmaceutical outpatient and hospital services, not subjected to ERP, which resulted in a price corridor between -81.7% and +96.3% (Kalo et al. 2015). In a Eurostat study in 2005, examining the prices of ten on-patent medicines in fifteen European countries from 2007 to 2012 in order to assess whether ex-factory prices of on-patented medicines in Western European countries have converged over a recent period, a price divergence between 2008 and 2012 was shown and is believed to have been driven by two countries, Germany, which has up to 27% more expensive pharmaceuticals than the average and Greece, which has up to 32% cheaper pharmaceuticals than the average (Eurostat 2005). All of the other 15 European countries studied had prices that centred on the average (Rémuzat et al. 2015). The observed price differentials can be partly attributed to the different pricing policies implemented in Europe (Toumi et al. 2014 and Rémuzat et al. 2015)

In the long-run, ERP was shown to result in some, but not substantial price convergence across European countries (Toumi et al. 2014 and Espin et al. 2014). Applying solely ERP as a pricing rule in a simulation exercise, led to a low average drug price decrease of about 15% in 10 years. The price differentials between countries remained substantial – around 30% – over these 10 years, suggesting a limited impact of ERP in price convergence.

Whether price convergence leads to higher or lower prices is determined by the ERP design such as the size of the basket, the ERP formula and the frequency of price revisions. Larger baskets, and an increase in basket size over time, are associated with some price convergence between European pharmaceutical prices (Leopold et al. 2012, BMI Germany 2011, BMI Switzerland 2010 and 2012 and Houy and Jelovac, 2014). It has also been argued that ERP can lead to

Table 13: ERP and association with price convergence: Summary of the available evidence

Issues	Overall Evidence	Studies	Countries with evidence	Quantifiable Impact
Price Convergence				
Ability of ERP to harmonize prices across countries	ERP when implemented across European countries, other OECD countries and the Middle East leads to some price convergence.	<ul style="list-style-type: none"> • OECD 2008 • Kalo et al. 2015 • Kanavos and VANDOROS 2011 • Espin et al. 2014 • Toumi et al. 2014 • Rémuzat et al. 2015 	<ul style="list-style-type: none"> • All EU countries • All OECD countries • Middle East countries • Canada 	<ul style="list-style-type: none"> • In the Middle East, the average price corridor is narrower for pharmaceuticals (-39.8%; +35.9%) than for outpatient and hospital services (-81.7%; +96.3%) (2014) • Price divergence between Germany, which has up to 27% more expensive pharmaceuticals than the average and Greece, which has up to 32% cheaper pharmaceuticals than the average
Price Convergence depends on ERP Design	The extent of price convergence towards European prices depends on the size of the basket and on the price considered in the ERP formula.	<ul style="list-style-type: none"> • BMI Germany 2011 • Leopold et al. 2012 • Houy and Jelovac 2014 • Toumi et al. 2014 	<ul style="list-style-type: none"> • All EU countries 	<ul style="list-style-type: none"> • As the basket of countries is increasing in size, ERP typically can induce price convergence towards the mean; • ERP can lead to a downward price convergence in Europe, when the lowest price in the basket is used to calculate the reference price.
Price Convergence depends on other exogenous factors	The extent of price convergence towards international prices depends also on exogenous factors such as possible currency fluctuations in Europe.	<ul style="list-style-type: none"> • Rémuzat et al. 2015 • Leopold et al. 2013 	<ul style="list-style-type: none"> • All EU countries 	<ul style="list-style-type: none"> • From 2007 to 2008 price divergence decreased in European countries, but increased from 2008 to 2012 due to currency fluctuations; • About half of the price differentials exceeded 50% in both EU and non-EU countries over time.
Short-term Vs. Long-term effect	There is weak evidence about the extent to which ERP results in substantial price convergence. Only four out of twelve studies examined whether ERP has a long-term impact on price convergence.	<ul style="list-style-type: none"> • Espin et al. 2014 • Toumi et al. 2014 • Rémuzat et al. 2015 	<ul style="list-style-type: none"> • All EU countries 	<ul style="list-style-type: none"> • Low average drug price decrease of about 15% at 10 years showed that the price differentials between countries remained substantial (around 30%) over these 10 years; • About half of the price differentials exceeded 50% in both EU and non-EU countries over time.

a downward price convergence in Europe when the lowest price in the country basket rather than the average price is used to calculate the reference price (Toumi et al. 2014).

With regards to exogenous factors affecting price convergence when ERP is applied, it has been found that currency fluctuations in Europe can have an effect on price convergence (Rémuzat et al. 2015). From 2007 to 2008 price divergence decreased in European countries, but increased from 2008 to 2012 due to currency fluctuations (Leopold et al. 2013). Other price mechanisms, such as price cuts, may also have an impact on price convergence (Rémuzat et al. 2015). However, the evidence synthesized in

this section is independent of other price schemes, as these regulations can be selective, i.e. for specific pharmaceuticals, or could be applied across the board.

3.3.4 Launch Delays

This endpoint examines the existence of delays in the launch of new pharmaceuticals in third countries as a result of ERP where launch delay is usually calculated as the difference in months between marketing authorisation and the country-specific launch date. Twenty-four studies were identified in the literature that studied the impact of ERP on the launch of new pharmaceuticals in third countries. Of

these, fifteen studies were peer-reviewed and nine were extracted from the grey literature. Nine studies were descriptive (WHO Guidelines 2013, Global Forum on Competition -GFoC 2014, Leopold et al. 2012, Vogler 2014, Vogler et al. 2015, BMI Taiwan 2012 and 2014, BMI Turkey 2015 and Mossialos et al. 2006), seven studies were both descriptive and empirical in nature describing ERP systems and their modalities and using post-only data from readily available sources and from IMS (Rémuzat et al. 2015, European Commission 2015, OECD 2008, Barros 2010, Kanavos et al. 2010, Vogler et al. 2016 and Europe Economics 2013) and an additional two descriptive studies referenced an empirical study with a regression model (Danzon et al. 2005) when studying launch delays in other countries (Håkonsen et al. 2009 and Espin and Rovira 2007). Three studies built a theoretical model to test how firms respond to the launch of their pharmaceuticals in countries implementing ERP (Danzon and Towse 2008, Houy and Jelovac 2013 and 2014) and one study performed a simulation exercise (Toumi et al. 2014). Finally, two studies were purely empirical using a regression model to test whether price regulation affects the launch of a pharmaceutical in particular countries (Danzon et al. 2005, and Kanavos and Vandoros 2011). From the twenty-four studies included in this endpoint, six papers provided long-term evidence on the impact of ERP on launch delays (Kanavos et al. 2010, Danzon et al. 2005, Håkonsen et al. 2009, Toumi et al. 2014, European Commission 2015 and Europe Economics 2013).

Launch delay is defined as “the months between the drug’s first global launch and launch in a specific country” (Kanavos et al 2010 and Danzon et al. 2005). Across the literature, the relationship between ERP and launch delay is ambiguous as the extent of these delays varies across countries (Kanavos et al. 2010, Håkonsen et al. 2009, Europe Economics 2013, Houy and Jelovac 2013 and 2014, Danzon et al. 2005).

Four issues were identified under this endpoint: the first is the impact of ERP on pharmaceutical launch in general, the second is whether ERP promotes launch sequencing, the third is the broader circumstances under which launch delays and launch sequencing can occur and the fourth is whether ERP affects launch.

Evidence shows that from 1994 until 1999, the three countries with the greatest number of launches were Sweden, Denmark and Germany, whereas the four countries with the fewest number of launches were Portugal, Italy, Greece, and Spain; the average launch delay, as defined above, ranged from 8.1 months in Germany to 17.4 months in Belgium (Danzon et al. 2005 and Håkonsen et al. 2009). The average delay for in-patent oncology pharmaceuticals was calculated for 2001-2013 using IMS data and a post-only design. Portugal had the largest launch delays and had to wait an average of 46 months for new oncology pharmaceuticals after their launch in other European markets. Switzerland and the Netherlands, on the other hand, had to wait just 5 months for the same oncology pharmaceuticals. For diabetic pharmaceuticals, Croatia had the longest delay at 37 months, while Switzerland again had one of the shortest delays at just one month. Five European countries with higher GDP, waited only about two months (Europe Economics 2013).

“Launch sequence strategy” is used by manufactures as a strategy to delay or avoid launching of new pharmaceuticals in countries with lower prices and/or low sales volume, especially if these are small markets referenced by countries with larger markets (Rémuzat et al. 2015; Leopold et al. 2012; OECD 2008; European Commission 2015; Toumi et al. 2014; Kanavos et al. 2010). For instance, manufacturers may strategically delay launching of a new drug in a lower-price country if the country’s prices will decrease prices in higher-price countries due to ERP (Europe Economics 2013, Houy and Jelovac 2013 and 2014, Danzon and Towse 2008, Danzon et al. 2005, Vogler 2014, Vogler et al. 2015, Vogler et al. 2016).

Evidence on launch sequencing strategies due to ERP is available from a post hoc assessment of secondary data arising from the relevant literature on time to market access for innovative drugs in Europe and the price levels of pharmaceuticals in 33 EU countries. This assessment showed that in Belgium, companies systematically delayed dossier submission in order to avoid the Belgian price (i.e. typically not among the highest within the EU) (Rémuzat et al. 2015). Furthermore, market research reports (based on sources such as regulatory agencies, pharmaceutical trade associations and information from market

Table 14: ERP and launch delays: Summary of the available evidence

Issues	Overall Evidence	Studies	Countries with evidence	Quantifiable Impact
Launch Delays				
Impact of ERP on pharmaceuticals launch	ERP has an unambiguous impact on the timing of pharmaceutical launch across countries.	<ul style="list-style-type: none"> • Kanavos et al. 2010 • Danzon et al. 2005 • Håkonsen et al. 2009 • Houy and Jelovac 2013 • Houy and Jelovac 2014 • WHO 2013 • Europe Economics 2013 • Espin and Rovira 2007 	<ul style="list-style-type: none"> • All EU countries • Switzerland • USA • Australia • Canada • Mexico • South Africa • Japan • New Zealand 	<ul style="list-style-type: none"> • The average launch delay ranged from 8.1 months in Germany to 17.4 months in Belgium (in mid 1990s) • Portugal had to wait an average of 46 months for new oncology drugs. Switzerland and the Netherlands had to wait just for 5 months (2001-2013) • For diabetic pharmaceuticals, Croatia had the longest delay at 37 months, while Switzerland again had the shortest delay of just one month whereas, five European countries waited only about two months (2001-2013)
Impact of ERP on launch sequencing	Manufacturers are adopting launch sequence strategies to delay launching of new pharmaceuticals in countries with lower prices and strict regulations	<ul style="list-style-type: none"> • Rémuzat et al. 2015 • Leopold et al. 2012 • OECD 2008 • European Commission 2015 • Toumi et al. 2014 • Kanavos et al. 2010 • Europe Economics 2013 • Houy and Jelovac 2014 and 2014 • Danzon et al. 2005 • Vogler et al. 2014, 2015 and 2016 • Danzon and Towse 2008 • BMI Taiwan 2012 • BMI Taiwan 2014 • BMI Turkey 2015 • WHO 2013 • Espin and Rovira 2007 • GfOC, 2014 • Kanavos and Vitoros 2011 • Mossialos et al. 2006 	<ul style="list-style-type: none"> • All EU Countries • Turkey • Taiwan 	<ul style="list-style-type: none"> • In Belgium, companies systematically delayed dossier submission in order to avoid the Belgian price • In Taiwan and Turkey manufacturers' are reluctant to launch new medicines • Lower income Eastern and Southern European countries tend to face longer launch delays than their Western and Northern European counterparts • During the mid-to-late 1990s, Greece, Belgium and France, had the longest average delay, between drug approval and marketing, whereas, Germany, the US and the UK, had the shortest average delay • Manufacturers listed countries with the least interventionist pricing system (United Kingdom, Germany and Sweden) as preferable for product launch initiation, in contrast to countries with smaller markets, such as Cyprus or Malta, or with lower disposable income, such as Poland, Bulgaria, Lithuania, Latvia, Estonia, Hungary and Romania which are also associated with price regulation through ERP.

Continued

Table 14 continued: ERP and launch delays: Summary of the available evidence

Issues	Overall Evidence	Studies	Countries with evidence	Quantifiable Impact
Launch Delays				
Launch delays and launch sequencing depend on other factors	Evidence on the pharmaceutical launch time varies considerably across countries depending on various features such as the country's disposable income, the size of the market and the regulation setting as well as the price levels that can be acquired by manufacturers.	<ul style="list-style-type: none"> • Kanavos et al. 2010 • Danzon et al. 2005 • Håkonsen et al. 2009 • Houy and Jelovac 2013 • Houy and Jelovac 2014 • WHO 2013 • Europe Economics 2013 • Espin and Rovira 2007 	<ul style="list-style-type: none"> • All EU countries • Switzerland • USA • Australia • Canada • Mexico • South Africa • Japan • New Zealand 	<ul style="list-style-type: none"> • Countries with lower than expected prices tend to have fewer products launched and longer delays; • Countries with extensive regulation tend to get access to new drugs relatively later than those with fewer regulations; • Lower income countries tend to face longer delays.
Short-term Vs. Long-term effect	50% of (n=8) the identified studies present long-term evidence on whether ERP affects pharmaceutical launch over a period of time.	<ul style="list-style-type: none"> • Europe Economics 2013 • Kanavos et al. 2010 • Danzon et al. 2005 • Håkonsen et al. 2009 • Toumi et al. 2014 • EC 2015 	<ul style="list-style-type: none"> • All EU countries • Switzerland • USA • Australia • Canada • Mexico • South Africa • Japan • New Zealand 	<ul style="list-style-type: none"> • From 1994 until 1999, the three countries with the most launches were Sweden, Denmark and Germany, whereas the four countries with the fewest launches were Portugal, Italy, Greece, and Spain • From 2001 to 2013, Portugal had the largest launch delays for in-patent oncology pharmaceuticals • During the mid-to-late 1990s, Greece, Belgium and France, which regulate launch prices, had the longest average delay between drug approval and marketing, whereas, Germany, the US, and the UK, which do not regulate launch prices and do not require price approval before launch, had the shortest average delay

research firms that is in the public domain) on Taiwan (BMI Taiwan 2012; BMI Taiwan 2014) and Turkey (BMI Turkey 2015), in the context of providing a country specific pharmaceutical market, regression based forecasts have expressed concerns that manufacturers might be reluctant to launch new medicines as they will be immediately subjected to low prices.

Lower income Eastern and Southern European countries, which implement stricter price regulations, also tend to face longer delays than their Western and Northern European counterparts with higher GDP per capita and wealthier markets (Europe Economics 2013, Houy and Jelovac 2013 and 2014).

Therefore, countries having lower than expected prices tend to have fewer products launched and face longer launch delays (Danzon et al. 2005, Kanavos et al. 2010, WHO 2013, Espin and Rovira 2007 and Global forum OECD 2014). This phenomena may also relate to longer bureaucratic processes required to reach price agreements with governments.

On the contrary, some high-income countries such as France experience short delays in the launch of their pharmaceuticals, considering that manufacturers weigh the opportunity costs of launch delay and that their incentive for prompt launch of potentially high volume products dominates any incentive of regulators to delay the launch of high volume

products that could have disproportionate budget impact (Danzon et al. 2005).

Pharmaceutical firms may also delay launching their products in a country due to the ERP policy itself, in reaction to strict ERP policies or in situations where they assume that the price of their product will be prohibitively low in a particular market. Consequently, manufacturers will often launch innovative pharmaceuticals in countries where they are free to set market entry prices and have less strict regulations compared to countries with smaller markets or with lower disposable income, where they will delay launch in order to increase prices in the reference basket (Leopold et al. 2012, European Commission 2015, OECD 2008, Europe Economics 2013, Danzon et al. 2005 and Kanavos et al. 2010, Kanavos and Vardoros 2011, Mossialos et al. 2006, Global Forum on Competition – GFoC 2014). For instance, during the mid-to-late 1990s, Greece, Belgium and France, which regulate launch prices, had the longest average delay, between drug approval and marketing, whereas, Germany, the US and the UK, which do not regulate launch prices and do not require price approval before launch, had the shortest average delay (Danzon et al. 2005). In addition, a study by the EC showed that when manufacturers were asked about their preferences for launching a new product they listed countries with the least interventionist pricing

system (i.e. United Kingdom, Germany, Sweden) as preferable for product launch initiation, in contrast to countries with smaller markets, such as Cyprus or Malta, or with lower disposable income, such as Poland, Bulgaria, Lithuania, Latvia, Estonia, Hungary and Romania, which are also associated with price regulation through ERP (Kanavos et al. 2010).

With regards to the factors affecting launch delays when ERP is implemented, European countries seem to be more exposed to spillover effects than non-EU countries and this is because of the existence of parallel trade among European Member States, the majority of which implement ERP formally or informally to inform prices of pharmaceuticals. The interdependence of European countries gives an additional incentive to manufacturers to launch new pharmaceuticals in high-price countries first and to delay launch, or even prevent launch entirely, in low-price countries (Barros 2010). Moreover, parallel trade effectively arbitrages price differences across countries and thus, has a similar effect to ERP in terms of compressing price differences and inducing strategic launch behaviour by firms (Kanavos et al. 2010 and Leopold et al. 2012). However, it has been noted that it is difficult to assess the extent to which strategic launching used to limit ERP spillover effects is delaying the launch in low-priced countries, as other factors are usually simultaneously present (i.e. parallel trade) (Rémuzat et al. 2015).

4. IMPACT ASSESSMENT OF ERP: A SYNTHESIS

4.1 METHODOLOGICAL APPROACH

In this section we summarise the overall direction and quality of evidence considered in this systematic literature review and perform an assessment on the impact of ERP as observed by the currently available literature. A simple vote-counting methodology was used, in order to determine the accumulated impact of ERP on each endpoint and issues identified within each endpoint. As such, an overall scorecard was developed, based on three dimensions: first, the direction of impact (i.e. positive or negative) that ERP was found to have on the endpoints and issues identified; second, the quality of the empirical evidence considered under individual endpoints and issues; and third, the extent to which the studied endpoints and issues have been examined explicitly in the available literature. In this context the endpoints we are concerned with relate to the policy objectives of country governments', as opposed to the objectives of any other potential stakeholders.

With regards to the direction of impact of ERP, the "+" sign indicates that ERP contributes to achieving the stated goals whereas the "-" sign indicates that it does not contribute to achieving the stated goals. The sign "+/-" is used in those cases where the impact of ERP on the relevant endpoint and issue is ambiguous. This is generally observed when the impact of ERP depends on other factors, such as the modalities of ERP methodology or other exogenous factors. Under this dimension, the simple-vote counting methodology was performed by counting the number of the identified studies providing positive evidence and the number of those providing negative evidence.

The overall quality of the identified empirical evidence has been classified as High=●, Moderate=◐, Low=◑, Very low=◒ and Not Available=○, based on the grading of evidence and recommendations in healthcare as presented by Schünemann et al. (2003). During the vote counting only studies examining each endpoint/issue empirically were considered for quality assessment. As discussed in the methodology section (see section 2.3), some studies referencing evidence collected by a post-only design were classified as very low=◒, whereas studies performing a regression analysis were considered as of low quality=◑. In the unlikely case of a study using a quasi-experimental design

or a difference-in-differences methodology being identified, the quality of evidence such studies presented was classified as High=●. Under each endpoint/issue, when different types of empirical studies were considered, the quality of evidence was then assessed according to the majority. For instance, when empirical evidence under an endpoint was given by three studies using a post-only design and only by one study using a regression analysis design, then the quality of empirical evidence under this endpoint was still considered as very low.

The third column represents an overall estimation of the strength of evidence on whether enough evidence was identified in terms of number of studies yielded regardless of their quality. A grading system similar to the one used in the quality of evidence dimension is also provided here, denoted by the number of studies included under each endpoint and the identified key issues; if the evidence presented under each endpoint/issue was derived from twenty-two or more studies, the strength of this evidence was classified as High=●; from fifteen to twenty-one as Moderate=◐; from eight to fourteen as Low=◑; from one to seven studies as Very Low=◒; and zero studies as Not Available=○. Finally, the last column describes the length of the relevant evidence. In other terms, it describes whether the evidence provided under each endpoint/issue examined the short or long-term (denoted by "S" or "L" respectively and "S/L" where there is both short and long-term evidence) impact of ERP.

Table 15 summarises the evidence on the impact of ERP within countries for the identified endpoints and issues, while Table 16 summarises the same evidence across countries, endpoints and issues identified for this purpose.

4.2 IMPACT OF ERP AT COUNTRY LEVEL

4.2.1 Cost Containment

Our findings suggest that ERP has delivered cost-containment, at least in the short-term, but the likelihood of generating greater savings in the longer term following introduction depends largely on the methodology of ERP applied, on the existence of other demand-side policies in place and on the

Table 15: Overall direction of evidence and quality of existing evidence on the impact of ERP within a country's borders

Study Endpoints	Issues identified within endpoints	Impact of ERP Positive(+) Negative(-) or ambiguous (+/-)	Quality of empirical evidence on the impact of ERP (where applicable)**	Overall strength of evidence on the impact of ERP**	Duration evidence applies to: Short-term (S) or Long-term (L)
Cost-Containment	Generating Healthcare Savings	+			S
	Healthcare savings depend on ERP Design	+/-			
Prices	Lower Pharmaceutical Prices	+			S/L
	Pharmaceutical prices depend on ERP Design	+/-			
	Pharmaceutical prices depend on market features	+/-			
Drug Use	Containment of consumption	+/-*			S
Availability	Market withdrawal	+			S/L
	Launch delays, launch sequencing or no launch	+			
Affordability	Affordability in HICs	+/-			N/A
	Affordability in LICs	-			
	Scope for increasing affordability	+			
Equity	Social welfare improvements	-*			N/A
	Prioritising of policy objectives	-			
Efficiency	Affordable prices (through price revision)	+*			S
	Stable share of drug spend on total health spend	+			
	Containing costs while guaranteeing access to medicines	+/-*			
Industrial Policy & Innovation	Incremental innovation and investment in (incremental) R&D	-			S
	Generics' entry and penetration	-			
	Influencing manufacturing and/or R&D investment decisions	+*			
	Innovation reward	+			
Overall		+			S

Source: Synthesis of the literature by the authors

* Inconclusive evidence

** High = , Moderate = , Low = , Very low = , Not Available =

additional cost-containment policies implemented in the country and in the referenced countries. In our report, empirical evidence of cost-savings generated through ERP has been observed for Slovakia and Turkey. The majority of the studies yielding evidence for this endpoint and the subsequent issues that were identified were descriptive, using data collected by a post-only design. As a result, the validity of the evidence provided and the quantifiable impact of ERP on healthcare savings are limited and could be subject to criticism. Only three out of seven studies assessed the ability of ERP to generate healthcare savings over time. Therefore, the strength of evidence on the impact of ERP on cost containment is weak and the quality of evidence is low.

4.2.2 Price levels

Overall, across Europe, ERP has been shown to put downward pressure on pharmaceutical prices at least in the short-term – only nine of the twenty-six studies considered long-term evidence. Examples from the Netherlands, Moldova, Bulgaria and Greece have been illustrated in the results section, giving examples of quantifiable evidence on the impact of ERP on pharmaceutical price levels. ERP is ‘path dependent’ and the extent of pharmaceutical price decrease depends firstly on the methodology of ERP applied and secondly on the aspects of the market in which it is applied. Eleven of the twenty-six studies under this endpoint used quantitative data to study the impact of ERP on pharmaceutical prices. The majority of the studies presenting evidence for this endpoint and its subsequent issues were descriptive studies using data collected by post-only analyses. Furthermore, two studies were purely empirical using a regression model, which can also be characterized as weak evidence.

4.2.3 Drug Use

Overall, due to limited evidence, no robust conclusion can be drawn about the impact of ERP on drug consumption, although evidence from one country has demonstrated that ERP is unlikely to diminish consumption of medicines as this is a factor influenced by external, demand and/or supply side variables. In conclusion, the strength of evidence on the impact of ERP on drug use is weak and the quality of evidence is low.

4.2.4 Availability

A significant body of evidence exists with regards to the impact of ERP on availability of medicines within countries. Overall, decreased availability was not recognised as an immediate outcome of ERP, but the low levels of prices generated by ERP policies might incentivise manufacturers to delay the launch of pharmaceuticals or even withdraw these from the market, resulting in unavailability and poor access to medicines, especially in low income/small market countries (which constitute reference countries for larger markets) and/or in countries with highly regulated pricing at the ex-factory level. However, despite the relative wealth of studies found compared to other endpoints specific to the impact of ERP within a country, evidence about the quantifiable impact of ERP on market withdrawal and/or launch delays of pharmaceutical products is of very low quality and inconclusive to support the claims about the unavailability of medicines arising due to ERP.

4.2.5 Affordability

Moderate evidence was found about the impact of ERP on affordability of medicines within a country. Overall, literature was directed towards the perception that ERP policies pay little attention to affordability within a country, with a significant impact on LICs. However, little empirical evidence exists in the current literature to quantify the extent to which affordability of medicines is affected as a result of ERP policies. Furthermore, no empirical evidence was found to assess how affordability could be improved if international comparisons were to be made at an average exchange rate or on the basis of PPPs or if policy makers in LICs employ confidential agreements to obtain lower effective prices through rebates or discounts.

4.2.6 Equity

The body of evidence is moderate with regards to the impact of ERP on the context of equity. Overall, country specific social welfare and equitable healthcare systems among countries will most likely be undermined following ERP implementation. A very limited body of evidence, largely descriptive in nature, suggests that ERP does not typically reflect

goals and priorities of the health system in which it operates, that it may shift the welfare equilibrium within a country due to higher pricing and that subsequent affordability issues arise as a direct consequence of ERP. Further empirical evidence is required in order to understand and quantify the impact of ERP from a societal perspective.

4.2.7 Efficiency

Literature relevant to the impact of ERP on efficiency is scarce and inconclusive. Overall, considering the very limited body of relevant evidence found, we conclude that even though there might be scope for ERP to lead to more affordable prices, increase efficiency via cost containment and reduce the proportion of pharmaceutical expenditure as a ratio of the total health care spending, especially when frequent price revisions of listed drugs take place, further research is still needed to evaluate and/or measure the overall impact of ERP in achieving multiple healthcare system goals such as addressing budget impact in the context of promoting accessibility to medicines.

4.2.8 Industrial Policy

Mixed evidence was found when assessing the industrial impact of ERP. Overall, according to limited empirical evidence, ERP has been shown to pose threats to industrial innovation and investment in research and development, mainly due to the reduced revenues it generates for manufacturers, its intricate association with parallel trading and the lack of transparency in the determinants underscoring the price set up. Overall, the available empirical evidence is of very low strength and quality making it difficult to draw distinctly positive or negative conclusions about the effects of ERP on industrial incentives.

4.3 INTERNATIONAL IMPACT OF ERP

4.3.1 Impact across borders

Extensive evidence was identified in the literature regarding the general cross-country spillover effects caused by ERP. As the majority of countries reference each other when calculating the external referencing price, spillover effects have caused unexpected consequences in countries applying ERP. Examples from Greece and Switzerland highlight the

substantial spillover effects of ERP across borders. Three out of ten studies under this endpoint used empirical evidence by post-only and regression analyses and only four studies examined whether the spillover effects are caused over time or only in the short-term due to ERP implementation. Thus, the strength and the quality of evidence under this endpoint can be considered low.

4.3.2 Price stability

Evidence on whether ERP leads to price stability is very limited and not very well understood. Few studies concluded that ERP most likely leads to price instability across countries, as price fluctuations in one country trigger price fluctuations in another country, leading to higher prices and lower availability of medicines. ERP is a tool used to regulate pharmaceutical pricing across countries, therefore its potential to stabilize pharmaceutical prices across countries should be high. However, the evidence gathered from the literature shows that prices indeed fluctuate due to numerous reasons, such as the market characteristics, the design of ERP, currency fluctuations and other regulations applied in each country causing price instability across countries. The strength of evidence under this endpoint is low. Finally, the identified empirical evidence uses weak methodological designs such as regression analysis models, resulting in low quality of evidence and lack of quantifiable evidence on the ability of ERP to result in price stability across countries.

4.3.3 Price Convergence

Price convergence is likely to occur when ERP is implemented across countries. The collected evidence showcased that ERP systems are expected to reduce the pricing differentials, but there are examples where price divergence is also observed. Evidence on the quantifiable impact of ERP on price harmonization across countries was presented from Germany and Middle Eastern countries. The strength of evidence under this endpoint is relatively high compared to other endpoints. However, the long-term impact of ERP on price convergence remains unclear as only four studies examined the link between ERP and price convergence over time.

4.3.4 Launch Delays

ERP affects the launch of pharmaceuticals across countries. Evidence in the literature varies considerably across countries depending on various determinants such as the country’s disposable income, the size of the market and the regulation setting as well as the price levels that can be deliberately adjusted by the manufacturers. Therefore, there are numerous countries where manufacturers are willing to launch their product as soon as possible and other countries where manufactures significantly delay the launching of new pharmaceuticals. As shown extensively throughout the literature, this phenomenon results in spillover effects across countries by limiting the

access and availability of medications in smaller countries, in countries with low price levels, in countries with stricter price regulations or those who must wait for many other countries to make a decision on reimbursement and on the price. Therefore, although ERP aims to deliver better control of prices and faster price erosion, it might also lead to unwanted effects, such as triggering pharmaceutical companies to increase the list price in order to avoid both the impact on the company’s revenues of ERP and the phenomenon of parallel trading (Rémuzat et al. 2015). Even if the quality of evidence under this endpoint is relatively weak (i.e. arising from a post-only analysis and two regression models which assessed the extent to which price regulations affects launch timing), there are a few

Table 16: Overall direction of evidence and quality of existing evidence on the impact of ERP across a country’s borders

	Study Endpoints	Issues identified within endpoints	Impact of ERP Positive (+) Negative (-) or ambiguous (+/-)	Quality of empirical evidence on the impact of ERP (where applicable)*	Overall strength of evidence on the impact of ERP*	Duration evidence applies to: Short-term (S) or Long-term (L)
International impact of ERP	Impact of ERP across borders	Impact across borders	+			S
		Implications of spillover effects	+/-			
	Price Stability	ERP ability to promote price stability across countries	+/-			L
		Price stability depends on market characteristics	+/-			
		Price stability depends on ERP design	+/-			
	Launch Delays	Impact of ERP on pharmaceuticals launch	+/-			S/L
		Impact of ERP on launch sequencing	+/-			
		Launch delays depend on other factors	+/-			
	Price Convergence	Ability of ERP to harmonize prices across countries	+			S
		Price Convergence depends on ERP Design	+/-			
		Price Convergence depends on other exogenous factors	+/-			
	Overall			+/-		

Source: Synthesis of the literature by the authors

* High = , Moderate = , Low = , Very low = , Not Available =

examples in the literature which showed the long-term measurable impact of ERP on the launching of pharmaceuticals. Therefore, any interpretation of results stemming from the literature on “launch delays” should be cautiously interpreted, whereas a better understanding is needed of the reasons behind the pharmaceutical launch delays and whether these delays are experienced over time in the presence of ERP (Espin and Rovira 2007).

4.3 METHODOLOGICAL LIMITATIONS

This literature review encountered some methodological limitations. Firstly, evidence from the grey literature has been used in order to ensure that all relevant studies have been considered. This may have resulted in the reduction of publication bias, but the inclusion of grey literature may also result in a less reliable systematic literature review. Secondly, the literature was scanned using online databases, where the results were limited to the English language. As a result, relevant papers published in a foreign language would have been excluded. Thirdly, variability in the quality of the papers collected to assess the impact of ERP was observed. This may have resulted in reduced scientific validity and reliability of our conclusions on the impact of ERP. Fourthly, availability bias could not be avoided as more evidence was found on some endpoints relative to others. Therefore, the impact on a particular endpoint might not have necessarily been worse, but rather better documented. Fifth, evidence from some of the yielded papers used in this systematic literature review are unavoidably old, therefore they might refer or capture out-dated ERP systems. Sixth, due to the nature of this analysis, a limited number of the publications collected from the systematic literature search commented on ERP system change over time and resulting impact on the studied endpoints. Finally, the effect of ERP as an individual policy is very difficult to isolate in the presence of other policy regulations implemented within the country but also implemented in the reference countries. Furthermore, as pharmaceutical pricing policies are constantly undergoing changes and being updated, the evidence presented in this systematic literature review may not reflect the policy landscape in future years. However, this study provides a benchmark at a specific point in time for further comparisons to be undertaken in the future.

4.4 POLICY IMPLICATIONS AND WAYS FORWARD

Available evidence with regards to the impact of ERP on country specific health system goals suggests that the downward price convergence and subsequent reduced revenues for manufacturers can not only be detrimental for the availability of medicines within a country, but also discourages manufacturers from investing in industrial innovation, while incentivizing manufacturers to adopt “launch sequencing” strategies, whereby they try to avoid lower pricing by delaying the launch of new products in low price/low income countries or in countries with highly regulated pricing at ex-factory level. There may be government practices related to launch delay whereby countries rely on other markets to set their prices. In such cases, these countries must wait for drugs to launch in the countries they reference before they can set the price and launch the drug in their own country. Whilst out-with the scope of this paper it is important to note that there may be significant bureaucratic differences between countries in terms of entry of new pharmaceuticals into the country market. In addition, prescription pharmaceuticals are probably the only patent protected sector where prices can decline. As a result there can be launch delays that are unrelated to EPR systems.

The emerging theme from the current literature is that ERP does not seem to promote efficiency insofar as ERP does not typically reflect the goals and priorities of the health system in which it operates. It may shift the welfare equilibrium within a country due to higher, unaffordable pricing relative to GDP of the country but it cannot directly control or impact drug consumption.

Overall, the available evidence around the impact of ERP within a country’s borders was very limited compared to, for example, the sources that discussed the impact of ERP from a cross-country perspective. The quality of existing evidence on the impact of ERP within a country is classified by the authors as relatively weak in terms of quality, as it emerged from only a limited number of empirical studies (10 out of 76 studies included in total), the majority of which were based on qualitative analyses of survey data or regression analyses of observational data, which could not be controlled for bias and/or potential confounders by the authors. No relevant studies were found that assessed or quantified the impact of ERP by employing compelling econometric

methodological designs, such as time series or pre-post analyses. Therefore, based on the existing evidence, no robust conclusions could be drawn about the role of ERP within a country's borders.

At the international level, the evidence identified on ERP impact across borders was undoubtedly stronger compared to the evidence provided at the national level, showing that ERP causes spillover effects, price convergence, price instability and launch delays. Despite the relative wealth of evidence found about the impact of ERP across a country's borders, we conclude that the impact of ERP across a country's borders remains ambiguous, due to the limited number of existing empirical studies and their relatively weak research design

From the identified evidence, we can conclude that there is a bidirectional relationship between the impact of ERP within and across a country's borders. For instance, potential price convergence created by ERP reinforces narrow price ranges across countries, which sometimes is unfavourable for low-income countries that are facing price increases, generally towards the basket's average. Price harmonisation discourages manufacturers from investing in research and development and hinders the availability and the affordability of pharmaceuticals within a country. In addition, launch delays caused in third countries would result in unavailability of pharmaceuticals in some small and low-income countries. Launch delays are at the same time, most likely caused by the lower price levels resulted by ERP in a country. In addition, launch-sequencing strategies adopted by manufacturers can lead to limited availability and access of medicines in smaller markets or in countries with lower prices.

However, both the impact of ERP at national and international levels depend largely on the ERP design and on other exogenous factors. It has been explicitly stated in the literature that the country specific characteristics, such as the size of the market, the health regulations in place, such as other pricing mechanisms and the nature and design of the ERP system itself in each country, plays a pivotal role on the ERP impact within and across countries. Country GDP has an indirect relationship with ERP impact, for example, lower income countries experience longer launch delays compared to those with higher GDP. Lower income countries are also more susceptible to undesirable effects of ERP such as inflated medicines

prices compared to GDP levels. In addition, ERP has been criticized for "path dependence", suggesting that the features of the ERP system influence the overall outcome. For instance, ERP can lead to higher savings if the transaction prices, as opposed to list prices, are considered in the ERP formula. Regular price revisions in combination with exchange rate fluctuations can also lead to increased cost-containment when ERP is implemented, leading to lower price levels in a country. Second, the formula used to calculate ERP needs to be set more cautiously, using an average-based formula to promote affordability and availability of pharmaceuticals and improving price stability across countries. Third, the countries in the basket, as well as the size of the basket, should be selected cautiously such that exchange rate volatility causing price instability across countries can be minimized. Consequently, by modifying the design of the ERP system by revising prices yearly, by increasing the basket size and avoiding referencing countries with less strict price regulations, spillover effects experienced due to ERP could be eliminated. These suggestions for optimal ERP impact stem from the literature analysed in this systematic review. They are broadly in line with a set of 14 principles recommended for the development of an 'ideal' ERP system across countries which are discussed in more detail in another paper in this series which outlines the implementation of ERP systems in a number of countries (Kanavos et al., 2017).

Overall, the evidence presented in this systematic literature review is classified by the authors as poor in terms of quality, as it comprised only a limited number of empirical studies (10 out of 76 studies included in total), some of which were based on qualitative analysis of survey data or regression analyses of observational data, where bias and/or potential confounders could not be controlled for by the authors. Of the 76 studies included, only 12 studies examined the impact of ERP against the studied endpoints and issues over the long-term (i.e. a study period of five years and more). As the majority of the evidence considered in this systematic literature review is short-term in nature, no major conclusions can be drawn from this review. Overall, robust research using empirical evidence with strong methodological design and a longer time horizon is urgently needed to understand and eventually interpret the drivers that influence the impact of ERP within and across countries.

5. CONCLUSIONS

We have conducted a systematic literature review in order to analyse the available evidence on the impact of ERP on a number of health system goals and the possible cross-country spillover effects. In the literature the following trends have been observed: i) at the national level, when ERP is implemented, health expenditure can be reduced at least in the short-term because prices are more likely to decrease, ii) the availability of pharmaceuticals, the equitable access to medicines and the stimulation of industrial policy, can be undermined when ERP is used to inform prices in a country and iii) the impact of ERP on the affordability of medicines is ambiguous. However, key endpoints, such the aforementioned relating to the macro level performance of health policy regulations, need to be examined side by side rather than individually, as they reflect a system-wide assessment.

At the international level, the country setting along with the methodology used in ERP can trigger cross-country spillover effects, resulting in price instability, leading to launch delays and unwillingness of manufactures to launch in low price countries, while promoting price convergence towards the international average. However, if we take into consideration that the evidence we found was weak in terms of quality, it is likely that the above observations arising from the currently available literature, should be taken with caution and could be interpreted otherwise if different study and methodological designs were to be employed.

Therefore, the findings from this systematic literature review are inconclusive and there is an unquestionable unmet need both on how ERP systems should be designed in order to attain a positive impact of ERP on a number of government policy goals within and across countries and on quantifying its impact.

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APPENDIX I

Table 17: Search Terms used in Systematic Literature Review

Database	Search Term 1	Search Term 2
Web of Science (WoS), CINAHL, EconLit, Medline, ProQuest, Cochrane Library and Scopus	"Pharmaceutical Price Regulation" OR	<i>drug OR</i>
	"Pharmaceutical Regulation" OR	<i>drugs OR</i>
	"Cost Containment" OR	<i>medicine OR</i>
	"Pharmaceutical Pricing"	<i>medicines OR</i>
	"External Reference Pricing" OR	<i>pharmaceutical OR</i>
	"External Price Referencing" OR	<i>pharmaceuticals</i>
	"International Price Comparisons" OR	
	"International Reference Pricing" OR	
	"International Price Referencing"	
WHO, WHO CC, OECD, European Commission databases	"External Reference Pricing" OR	
	"External Price Referencing" OR	
	"International Price Comparisons" OR	
	"International Reference Pricing" OR	
	"International Price Referencing"	

APPENDIX II

Table 18: Comparison between the scope of study and endpoints included in other systematic literature reviews

Identified Systematic Literature Reviews	Scope of the Study	Endpoints included
Rémuzat, C., Urbinati, D., Mzoughi, O., El Hammi, E., Belgaied, W. and Toumi, M., 2015. <i>Overview of external reference pricing systems in Europe</i> . <i>Journal of Market Access & Health Policy</i> , 3.	An overview of ERP systems in Europe both on processes and potential issues in all European countries including Iceland, Norway, and Switzerland.	<ul style="list-style-type: none"> (i) ERP processes in Europe (ii) National legal framework (iii) Scope of ERP (iv) Composition of the country basket (v) Price calculation and selection of reference products (vi) Limitations of ERP (vii) Potential consequences of ERP, including : <ul style="list-style-type: none"> a. spillover effects and price convergence b. patient access to medicines c. affordability and d. industry revenue and sustainability.
<i>The Impact of External Reference Pricing within and across a country's borders</i>	Study the potential of ERP as a mechanism of pharmaceutical price regulation within and across countries over the short- and the longer-term in a systematic way by bridging the gap between concepts, practice and impact.	<ul style="list-style-type: none"> (i) At country level: <ul style="list-style-type: none"> a. Cost-containment b. Pharmaceutical Prices c. Drug use d. Availability e. Affordability f. Efficiency g. Equity h. Industrial Policy (ii) At international level: <ul style="list-style-type: none"> a. Spillover Effects b. Price stability c. Price Convergence d. Launch delays in 3rd countries