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An Evaluation of Medicines Shortages in Europe with a more in-depth review of these in France, Greece, Poland, Spain, and the United Kingdom

by

birgli® ag

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1. Executive Summary

Medicine shortages have consistently been in the media over the past few years and have seemingly, with the economic crisis and austerity programmes, become a crisis in their own right.

Many have laid the blame squarely in one area or another with almost casual references to others. Our review shows the causes are quite varied and indeed vary according to market, time, product, and of course cause. Thus any particular case is actually only a snapshot of that specific case and may not apply to others.

This report seeks to shed a little more light on the causes behind shortages, current action to reduce shortages, and will propose a number of solutions (most of which are existing proposals from various parties) that stakeholders can review.

During the course of the research conducted, one item does appear to be consistent throughout and this is a lack of communication and coordination among all stakeholders affected. By stakeholders we are referring to Marketing Authorization Holders (MAH), Payers, Wholesalers, Pharmacies, Hospitals/Providers, Legislators/Authorities (member states and at EU level), and Parallel Distributors to name a few.

1.1. What this report does and does not present

Though shortages of medicines, based on the significant volume of reporting on the subject, appears to be a global issue, this report, will have a more specific focus on France, Greece, Poland, Spain, and the United Kingdom. References and analogies will be drawn from a number of other markets in particular the United States which appears to be furthest along the road to quantify the issue in their market.

Unlike many others currently circulating on the market, this report is not an analysis of the merits of the different distribution systems currently present on the market (wholesale, DTP, single channel distribution, direct to patient, etc.).

This report will also not review or debate the levels of healthcare cover patients throughout the five markets covered (and elsewhere) have a right to and at what cost. In other words, we will not attempt to define what “universal healthcare” means and what patient rights are in the area of access.

True quantitative data was very difficult to come by as evidenced by the PGEU and numerous other bodies¹². This is in part due to the extreme reluctance of the stakeholders

¹ Medicine Shortages in European Community Pharmacies, Ref 12.08.28E 003, PGEU



we met and discussed with to share the data that they have. The only way true transparency is to be achieved is if each stakeholder shares the information they have and discusses all the touch-points along the way.

1.2. Data collection

To ensure that we were able to achieve a more representative level of participation in the numerous interviews directly conducted, we have loosely applied Chatham House Rules. This means that though we will try to attribute all references directly to a source where we have been given permission, otherwise the references will be general.

2. Core Principals

2.1. Patients needs / rights

The rights to patients in Europe are enshrined in Article 81 of Directive 2001/83 which states that: “The holder of a marketing authorisation for a medicinal product and the distributors of the said medicinal product actually placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply Medicinal products so that the needs of patients in the Member State in question are covered”³.

This article is repeatedly referred to in virtually all the documentation reviewed whether official or reports/journals/articles.

There is no dispute that the patient should be the primary consideration in the discussion regarding shortages and the impact they have on his/her wellbeing and outcomes.

2.1.1. vs commercial aspects

Regardless of Article 81 of Directive 2001/83 there are structural issues that have arisen, in part exacerbated by the economic crisis in Europe. An article in 2012 in the Wall Street Journal puts it quite clearly that:

“as of February (2012), Greece, Spain, Portugal and Italy owed the pharmaceutical industry €15 billion”, this in the form of late payment for product consumed or purchased by providers⁴.

² APPG Pharmacy - Report of Inquiry Into NHS Medicines Shortages, 15 May 2012, <http://www.appg.org.uk/APPG%20Pharmacy%20-%20Report%20of%20Inquiry%20Into%20NHS%20Medicines%20Shortages.pdf>

³ Pharmaceutical Committee, 22 October 2012, 69th Meeting, Pharm 610, Agenda point 2.a), European Commission Health & Consumers Directorate General, http://ec.europa.eu/health/files/committee/69meeting/pharm610_shortages.pdf

⁴ Drug Firms Urge Price Action; Steep Discounts in 5 European Nations Create Shortages, 25 June 2012, Wall Street Journal, <http://online.wsj.com/article/SB10001424052702304870304577488041346373860.html>



Not only is there a significant issue of receivables from the payers of various markets, there is also a significant challenge with governments forcing down prices of pharmaceuticals in a number of markets to reduce spend and cost.⁵ Manufacturers with products on reimbursement lists have little choice in a regulated market but either to accept these mandated discounts or to delist their products.

2.1.2. Vs economic capacity

By economic capacity we refer to a country's capability to afford the healthcare it seeks. As briefly shown in earlier, some countries are currently not in a position to pay for their previous/current levels of healthcare provision, including medicines.

This raises significant questions surrounding patient access. With country payer systems no longer able to afford certain therapies, there is in principle a shortage of funding. This shortage of funding has resulted in pharmacies and hospitals not getting access to medicines due to payment issues and thus effectively resulting in shortages at market level. This effect has been seen in a number of markets, notably Greece, where pharmacies are unable to order due to payment issues and patients are unable to pay privately for treatment, while manufacturers (are forced to) consider the removal of products from the market and to delay or not to launch new products.^{6,7}

Economic capacity has been impacted by the economic crisis, but was also evidenced prior to the crisis and ensuing austerity.⁸ It is important to add, however, that many healthcare systems were already suffering from deficits, pricing, and other structural pressure prior to the crisis. The crisis made many of the pressures more visible.

2.2. Principle of pro-activity

Regulations currently in place in principle cover a significant level of proactivity. In a number of markets MAHs need proactively to inform the respective health authorities about shortages they are aware of due primarily to manufacturing or business decisions.^{9,10,11} Many current shortages in the market, however do not appear to be exclusively or directly linked to manufacturing or business reasons but with questions

⁵ The implications of international reference pricing and parallel trade on social welfare and patient access: Final Report, Charles River Associates, September 2012

⁶ Country Level Discussions/Interviews - birgli research:

⁷ The implications of international reference pricing and parallel trade on social welfare and patient access: Final Report, Charles River Associates, September 2012

⁸ Pharma access problems "putting EU at risk" World News | May 20, 2013, Lynne Taylor, http://www.pharmatimes.com/Article/13-05-20/Pharma_access_problems_putting_EU_at_risk.aspx

⁹ Policy review - birgli research - see links to policy covering this topic

¹⁰ Reflection paper on medicinal product supply shortages caused by manufacturing/Good Manufacturing Practice Compliance problems, European Medicines Agency, 22 November 2012, EMA/590745/2012, Patient Health Protection

¹¹ Lieferengpässe von Humanarzneimitteln, 26.04.2013, BfArM, <http://www.bfarm.de/DE/Pharmakovigilanz/Lieferengp/lieferengp-node.html>



related to distribution channel structures, parallel distribution, quotas, supply chain policy, and limited numbers of manufacturers among others being raised as possible causes. Current policy appears to have limited oversight in this area although in principle the same legislation would apply. Nevertheless, steps are being taken in this direction, as evidenced by various actions at country and European level.

2.3. Anticipation & Prevention

Patient welfare requires that they have access to the best possible care that can be provided under the national system they are covered by.

Shortages need to be anticipated and prevented to minimise the impact on patients. We will review various market mechanisms and proposals currently on the market.

3. Definition and categorisation of shortages

3.1. Word "shortages" is misleading

The term "shortages" is not broad enough to describe why or how long a particular product is affected. Furthermore, the term in different languages also have completely different connotations. In German the word "Defekt" is used by wholesalers implying a break down in a process and "Lieferengpässe" or delivery bottlenecks by the BfArM, the German medicines agency. In French the words used are "ruptures de stock" which implies a "disruption", while the use of the term by wholesalers is "manquant" meaning missing.

There does not appear to be a single word that would encompass all possible reasons behind a product shortage. However phrases would be more descriptive and perhaps useful. A simple suggestion would thus be to use short phrases to at least provide an indication towards the reasons that are in question and the word "shortages" to apply to all causes. Some possible phrases would be:

- Negative effects on the continuity of supply due to {list reason(s)}
- Unavailability at the point of dispensing due to {list reason(s)}

Without some form of quantitative/measurable and time-based component associated to a definition, however, we will continue to lack the ability to judge the severity and causes of shortages.

3.2. Primary reasons for shortages

Our review has led to a large number of reasons behind many of the supply issues today. Summarized in two main headings these are, but not limited to, as follows:



Table 1 : Reasons for Shortages¹²

Nr	Unpredictable	Nr.	Predictable
1.	Natural Disasters	1.	Product discontinuation
2.	Manufacturing problems	2.	Industry consolidation (M&A)
3.	Raw Material Shortages	3.	Limited manufacturing capacity
4.	Non-compliance with regulatory standards	4.	Just-in-time inventories
5.	Packaging shortages	5.	Rationing / quotas
6.	Unexpected demand	6.	Deliberate shortages to manipulate price
7.	Epidemics	7.	Market shifts
8.	Parallel distribution	8.	Launch of a new competitor, new formulation, or patent expiry
9.	Competitive issues		
10.	Foreign exchange effect		
11.	Sovereign issues (financial crisis, debt, default)		

There are market reports available on virtually each of the above, but based on our research and assessment, there are a few key areas which cover much of the above and which can be loosely grouped under the following key headings:

Economic, Business & Supply Chain

We again point out the challenge of getting quantifiable data in some areas, and of our general preference to avoid anecdotal “proof”. Based on lists of products that have a “breach in the continuity of supply” or are not immediately “available at the point of dispensing”, we can from our perspective safely assume that product is not where it should be when it needs to be there. Whether these can be defined as shortages is to some extent a matter of perspective.

¹² birgli research



We will thus review these key areas we have seen in our review from a European perspective and then in the five countries we have examined. There may be the concern of bias in the items we have selected to which we can only answer that our review is not exhaustive. We do, however, feel it is indicative of the general situation in Europe and the markets covered, and would add that there is not any importance to the order in which we discuss topics though the pieces do fit together.

4. Shortages - some causes and an analysis of these

4.1. Economic challenges and austerity

We are all acutely aware of the challenges all markets in Europe (and elsewhere) are facing today. Not a day goes by without headlines referring to them. Healthcare is often at the forefront of reporting in financially stricken countries, especially in the southern parts of Europe, which need to make significant cuts to their budgets. Some representative extracts from articles demonstrate this:

“UK manufacturers have reassured pharmacists that they will not face similar medicines shortages to Greece, following media reports of manufacturers withholding supply after the country ran up £1.7 billion in unpaid bills.”¹³

“The European Union (EU) is being put at risk because millions of patients in the region cannot afford their medicines, a leading EU politician has warned.”¹⁴

“The deepening economic crisis in the Euro-Zone has exposed health systems around the world, particularly in Europe, to public and private budgetary constraints. Healthcare systems currently face a funding crisis, which is adversely affecting health outcomes.”¹⁵

These are indeed challenging times. Governments have taken measures to reduce their spending in healthcare (not to discount other areas in their budgets). The net impact is quite clear through three primary measures (there are others); price reductions, reference pricing, and payment delays (whether voluntary or not)/ among other things in various markets:

¹³ UK will not face drug shortages like debt-ridden Greece, manufacturers say, James Waldron, 4 March 2013, Chemist and Druggist, http://www.chemistanddruggist.co.uk/news-content/-/article_display_list/15362918/uk-will-not-face-drug-shortages-like-debt-ridden-greece-manufacturers-say

¹⁴ Pharma access problems "putting EU at risk" World News | May 20, 2013, Lynne Taylor, http://www.pharmatimes.com/Article/13-05-20/Pharma_access_problems_putting_EU_at_risk.aspx

¹⁵ Acute or chronic: the impact of economic crisis on healthcare and health, July 2012, Volume Nine, KPMG.COM, <http://www.kpmg.com/DK/da/nyheder-og-indsigt/nyhedsbreve-og-publikationer/publikationer/brancher/healthcare/Documents/IssuesMonitor-July2012.pdf>



4.1.1. Price reductions & reductions in spending

A brief summary of some of the recent price reductions can be seen below:

Table 2: Price cuts undertaken in selected European Countries from 2010-2012¹⁶

Country	Time	Price reduction
Greece	May 2010, July 2011	22% average price cut followed by across the board cuts of 10% respectively
Ireland	February 2010	40% price reduction on off patent medicines. More followed in 2012
Portugal	October 2010	6% deduction on maximum retail price and further cuts in July 2012, including a new basket of reference countries
Spain	May 2010	Price reductions ranging from 0-30% according to price level for all off patent medicines
Poland ¹⁷	2012	Price reductions at pharmacy level of an average of 5.7% (average prices are already 43% lower than other EU markets and 59% for innovative drugs)

Similar action has been taken in a number of other markets and further action in those mentioned has also taken place and can be summarized as follows:

Table 3: Pricing Policy Measures 2010-2011

Pricing Policy Measures undertaken in EU countries in 2010 & 2011 ¹⁸				
Price reductions	Discounts, rebates, clawbacks/paybacks and other arrangements	International Reference Pricing	Planned changes in distribution remuneration	Changes in VAT on medicines
Czech Republic	Estonia Germany	Germany Iceland	Belgium Germany	Czech Republic †

¹⁶ The implications of international reference pricing and parallel trade on social welfare and patient access: Final Report, Charles River Associates, September 2012

¹⁷ Impact of the new Reimbursement Act on the Pharmaceutical Sector in Poland, 27 November 2012, IMS

¹⁸ Acute or chronic: the impact of economic crisis on healthcare and health, July 2012, Volume Nine, KPMG.COM, <http://www.kpmg.com/DK/da/nyheder-og-indsigt/nyhedsbreve-og-publikationer/publikationer/brancher/healthcare/Documents/IssuesMonitor-July2012.pdf>



Pricing Policy Measures undertaken in EU countries in 2010 & 2011 ¹⁸				
Price reductions	Discounts, rebates, clawbacks/paybacks and other arrangements	International Reference Pricing	Planned changes in distribution remuneration	Changes in VAT on medicines
Germany Greece Iceland Ireland Lithuania Malta Portugal Spain Switzerland Turkey UK	Italy Lithuania Poland Portugal Romania Spain	Lithuania Malta Slovakia Spain Switzerland	Greece Iceland Italy Latvia Lithuania Poland Portugal Spain Switzerland	Finland ⬆️ Greece ≈ Latvia ⬆️ Poland ⬆️ Portugal ⬆️ UK ⬆️

Governments have been successful in reducing their cost of medicines, but there have been some side effects of these policies.

Growing price disparities between various countries have led to “lower price” and “higher price” markets.

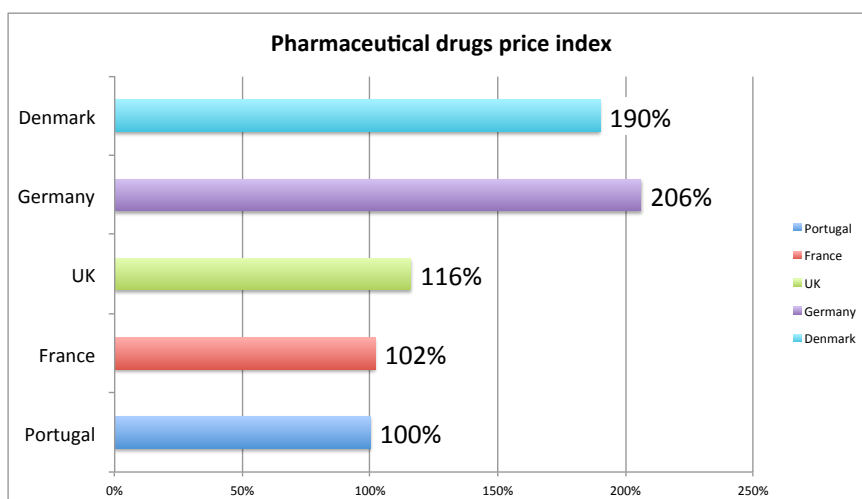


Figure 1: Pharmaceutical drugs price index - vs Portugal¹⁹

¹⁹ Caracterização e valorização do (des)abastecimento do mercado farmacêutico nacional, Relatório sumário, 10 Sept 2012, For Apifarma by Deloitte Consultores:
[http://www.apifarma.pt/salaimpresa/noticias/Documents/Apifarma_Desabastecimento_Relat%C3%B3rio_09102012%20\(2\).pdf](http://www.apifarma.pt/salaimpresa/noticias/Documents/Apifarma_Desabastecimento_Relat%C3%B3rio_09102012%20(2).pdf)



A similar review of 10 innovative products across a number of CEE markets provides further evidence of the differences between markets.

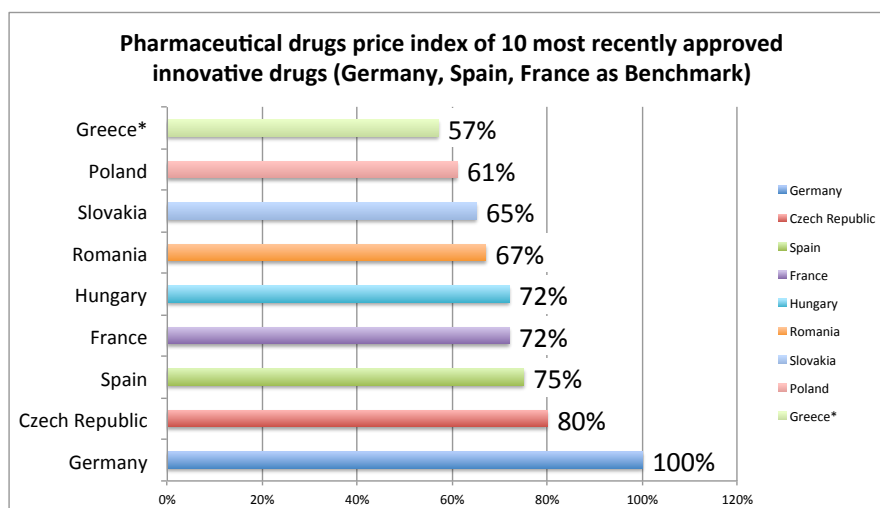


Figure 2: Pharmaceutical drugs price index²⁰ (*birgli estimate)

The effect of recent legislation on pricing can be seen in Portugal. In 2005, the price index with Portugal as a base of 100, Germany was indexed at 206²¹. In other words, due to the measures taken by the Portuguese government, German prices are now double those of Portugal on average in 2012.

Combined with significant price reductions, we can also see that government spending on pharmaceuticals has also been dramatically reduced in countries severely impacted by the crisis, but also in countries such as Poland which has been less so affected.

Selected impact of spending and price cutting measures

Spain €2.2 bn less in 2012 vs. 2008²²

Greece €1.65 bn less public spend on pharma in 2012 vs 2008²³

Poland €650m in Rx sales vs 2011²⁴

An in-depth review of price reductions and cost cutting measures would be beyond the

²⁰ European Turmoil 2012: A Review of Drug Prices and Market Access Across Europe, HIS Global Insight, Slide Share, <http://www.slideshare.net/IHS/drug-prices-andmarketaccessacrosseuropewebcasteuropeanturmoil2012>

²¹ Cost-containment policies in public pharmaceutical spending in the EU, Economic Papers 461, September 2012, European Commission, http://ec.europa.eu/economy_finance/publications/economic_paper/2012/pdf/ecp_461_en.pdf

²² Spain research by birgli

²³ Greece research by birgli

²⁴ Impact of the new Reimbursement Act on the Pharmaceutical Sector in Poland, Warsaw, 27 November 2012, IMS



scope of this paper and some of our bibliography items will provide a more in-depth view of each. These facts show that many other areas of the healthcare industry will be impacted including shortages, the main topic of this review.

4.1.2. International Reference Pricing

Price cuts in one or more markets has an impact beyond the countries, which have undertaken them, due to international reference pricing schemes in most markets in Europe. In effect if one country reduces prices, there is a fairly rapid ripple effect reducing prices in other markets.

Though reference pricing is nothing new, a recent article in the Wall Street Journal gives a glimpse into the dramatic effect cuts are having with Andrew Witty, CEO of GSK, pointing out that some 26 countries inside and outside Europe have reference pricing schemes that include Greece in their baskets. It is claimed that a 10% price cut in Greece may cost the industry just under €300 million in Greece but €800 million in Europe and up to €2.2 billion globally.²⁵

The following table details the list of countries in the EU with reference pricing in place. Each use different baskets of countries to make their calculations

Table 4: Reference Pricing in the EU²⁶

International Reference Pricing in the EU	
Countries with international reference pricing in place	BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IT, LT, LV, NL, NO, PL, PT, RO, SI, SK
Countries where reference pricing was abolished	SE
Countries who never introduced international reference pricing	AT, CY, IE, LU, MT, UK
Calculation of international reference prices	

²⁵ Drug Firms Urge Price Action; Steep Discounts in 5 European Nations Create Shortages, 25 June 2012, Wall Street Journal, <http://online.wsj.com/article/SB10001424052702304870304577488041346373860.html>

²⁶ VOGLER S., HABL C., BOGUT M. & VONČINA L. 2011. Comparing pharmaceutical pricing and reimbursement policies in Croatia to the European Union Member States. Croatian medical journal 52: 183-197.



International Reference Pricing in the EU	
Lowest price of products in the group	BG, CZ, DE, DK, EE, FR, HU, HR, IT, LT, LV, PL, RO, SI, SK
Below average of prices of products in the group	DE, ES, FI
Average price	BE, EL, NL
Above average	PT

The above shows that a reduction in the price in virtually any country in Europe can have rapid and dramatic effect in the pricing of products other markets. It also shows how interlinked the market is in Europe and that in fact, the pharmaceutical market is quite controlled. In essence many basic concepts of a free market, such as setting of prices, are at best marginally present in the pharmaceutical industry.

4.1.3. Delays in payment

Though delays in payment are possibly symptomatic of the financial crisis in general, their impact on the industry is dramatic. One can argue that the pharmaceutical industry, wholesalers, and pharmacies have in some countries financed the consumption of medication for periods, in some cases, exceeding twelve months.

Linked to the dramatic reductions in price undertaken by the various governments, are other closely linked developments. The first concerns delays in payment by payers (national insurance schemes) to pharmacies/hospitals which impacts on payment upstream. In a number of markets, payment delays have amounted to over 360 days. As of February 2012, Greece, Spain, Portugal, and Italy were essentially more than €15 billion overdue²⁰. Greece and Spain, in scope of this review, account for just under €8 billion of this amount²⁷.

In the case of France, Germany, Italy, the Netherlands, Spain, and the UK, wholesalers pre-finance the market on average up to €10.2 billion, a value equivalent to 41 days credit (most recently €10.4 billion and 44 days according to GIRP).²⁸

²⁷ birgli research

²⁸ Distribution profile and efficiency of the European pharmaceutical full-line wholesaling sector, Institute for Pharmaeconomic Research, Evelyn Walter, Aline Dragosits, Monira Said, January 2012.



Although we can say that governments have successfully reduced spending (to be reviewed in more detail later) through price cuts and other measures, all of these items put tremendous strain on the system. It should therefore not be a major surprise that there are repercussions, including shortages, throughout.

4.1.4. Tendering (in particular generics)

Tendering has been pointed out as another major development in a number of markets. Germany, the Netherlands, and Denmark have seen tender processes put into place which have significantly reduced prices of primarily generic products.²⁹ Although the markets we reviewed have limited tender procedures in place, they may take this practice up when seeing how other markets have reduced spend and the impact of reference pricing may nevertheless accelerate this process.

Tendering has effectively made a few markets considerably less interesting from a business perspective with the result that fewer companies are responding to requests for tenders and periodic shortages appearing for some lines of product as a result (including some companies being unable to meet the obligations of the tendering process).²⁷

4.1.5. Legislation supporting parallel distribution

Parallel distribution is supported by the authorities in a number of markets in their effort to reduce spend on medicine. Parallel distribution is thus not only a question of the free movement of goods enshrined in the EU, but part of a general effort to reduce cost. Below is a brief summary of markets where parallel distribution is directly encouraged:

Table 5: Policies to promote the use of parallel distribution (2004)³⁰

	Denmark	Germany	Netherlands	Norway	Sweden	United Kingdom
Pharmacy required to inform patients of the availability of parallel imported products	x	x			x	
Pharmacy quota on parallel import dispensing rates		x				
Financial incentives for pharmacy to dispense parallel imported drugs			x	x		x
Financial incentives for dispensing lower-price drugs in general, including parallel imported drugs				x	x	x

Reviewing the savings and economics behind parallel distribution are out of scope of this review. There are many documents to refer to on the subject.

²⁹ Leading Generics Manufacturer:birgli research

³⁰ Does pharmaceutical parallel trade serve the objectives of cost control?, Panos Kanavos and Stacey Kowal, Eurohealth Vol No 2, pgs 22-26, 2008, http://www.euro.who.int/__data/assets/pdf_file/0003/80445/Eurohealth14_2.pdf



4.2. Business

We have shown dramatic price cuts, the impact of reference pricing, and a brief glimpse into delays in payment on the industry. Each of these items have impacted decisions businesses have taken across the supply chain beginning with manufacturers and ending with pharmacies & providers. Many of these decisions have had a negative impact on shortages and can include the following:

4.2.1. Tightening of payment terms

In each of the markets where there have been significant delays in payment via the reimbursement system, there has been a consequent tightening of payment terms by manufacturers to wholesalers and pharmacies alike. In some cases this has resulted in providers going on “cash only” terms.

Most dramatically affected has been Greece, where pharmacies have in many cases been unable to purchase product for dispensing to patients. With pharmaceutical expenditure down about 50% in Greece and arrears in the area of €2 billion³¹, many wholesalers, pharmacies, and providers are on cash terms.³² The situation appears less dramatic in other markets but in Spain, Portugal, and other hard-hit markets, pharmacies struggle to get reimbursed and to pay wholesalers that has led to a tightening of terms and tighter availability of stock. Effectively shortages have arisen due to liquidity issues.

The impact of this tightening is not adequately documented or quantified though the data would be available from manufacturers, pharmacies, wholesalers, and hospitals.

4.2.2. Reduced product introductions and market withdrawals

4.2.2.1. Lower priced markets

A number of studies have shown that in lower price markets, the level of product introductions has decreased and in some cases delisted from markets entirely. In the case of Greece this has been clearly shown with 203 products withdrawn from the market in 2012 of which 25 have no generic equivalent.³³

Studies have, however, shown this to be the case in many markets, in particular smaller markets as well as lower priced ones. The following chart demonstrates a combined effect of lower priced markets and smaller markets versus larger and higher priced ones:

³¹ Greek firms blame govt as drug access "reaches breaking point" WORLD NEWS | MARCH 12, 2013
LYNNE TAYLOR

³² Greek Crisis Has Pharmacists Pleading for Aspirin as Drug Supply Dries Up, Naomi Kresge - Jan 10, 2012, <http://www.bloomberg.com/news/2012-01-10/greek-crisis-has-pharmacists-pleading-for-aspirin-as-drug-supply-dries-up.html>

³³ Greek firms blame govt as drug access "reaches breaking point" WORLD NEWS | MARCH 12, 2013
LYNNE TAYLOR, http://www.pharmatimes.com/Article/13-03-12/Greek_firms_blame_govt_as_drug_access_reaches_breaking_point.aspx

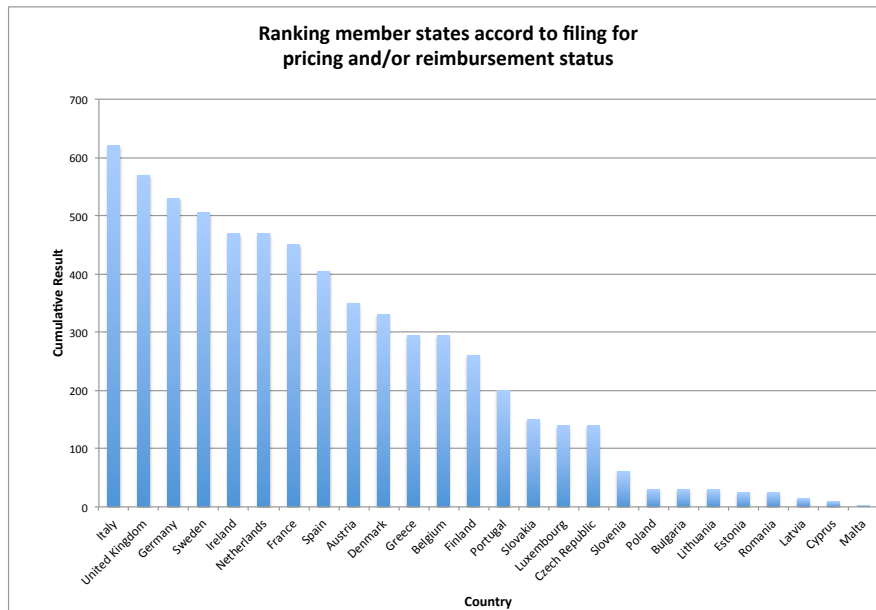


Figure 3: 2008 - filing for pricing and/or reimbursement status³⁴

A survey in 2012 showed a similar phenomenon for the introduction of innovative drugs. The correlation with the previous chart shows a link between size of market, pricing policy, and reference pricing. The smaller the market and/or with tighter pricing policy and reference pricing :

Table 6: Market Access: Availability of 70 innovative drugs approved by the EMA³⁵

Availability of Innovative Products	Type of market	Countries
41%	Fast Pricing procedure	Germany, UK, Norway, Denmark, Netherlands
14%-33%	Launch sequence based on priority and price optimisation	Romania, Slovenia, Luxembourg, Belgium, Spain, Austria, Sweden, France, Slovakia, Finland
< 12%	Lagging countries	Czech Republic, Italy, Ireland, Bulgaria, Cyprus, Estonia, Latvia, Greece, Hungary, Poland, Lithuania

³⁴ The implications of international reference pricing and parallel trade on social welfare and patient access: Final Report, Charles River Associates, September 2012

³⁵ European Turmoil 2012: A Review of Drug Prices and Market Access Across Europe, HIS Global Insight, Slide Share, <http://www.slideshare.net/IHS/drug-prices-andmarketaccessacrosseuropewebcasteuropetourmoil2012>



The business of pharmaceuticals has social dimensions that complicate how companies should operate in this sector. On the one hand, it is a fairly straightforward decision to place, market, and maintain a presence in countries where it makes financial sense to do so. On the other hand, social components make such decisions, which affect the health of citizens, complicated. We do not in any way judge companies making these decisions but when debts spiral out of control and price cuts affect a global business, at some point, something must give.

4.2.2.2. *Tender markets*

We have not reviewed the issues surrounding tenders in any great depth. Their impact, however, is no less corrosive to business than the previous discussion. There is an added level of complexity, due to rapidly changing suppliers between tenders, that makes business continuity difficult, and in some cases simply not attractive.

A case in point would be a major generic manufacturer required to supply product within two months of winning a tender and for which a minimum of 80% of the products shelf-life on delivery is stipulated. This, coupled with a monthly tender frequency is an unsustainable model. Some generic manufacturers have opted simply not to supply or respond to tenders, others have been unable to supply after successful tender, and providers hold minimal stock to ensure they are not left with the wrong product.³⁶

Tendering is a very complicated process, which would require a separate study to review.

4.2.3. *Parallel distribution*

Parallel distribution is often accused of being possibly the primary source for shortages. We have, however, just shown that there are other significant factors that weigh heavily on shortages and access to pharmaceutical products. The previous discussion shows that with significant differences in prices between the various markets and measures taken to control cost, parallel distribution will occur and is also encouraged by various countries.

We would also point out that, of the pharmacies and wholesalers, which have in many markets struggled to survive with declining margins, some will look to parallel distribution to boost income.

Continuous prices reductions, with minimal regard on the impact this has on companies and whether a market remains tenable, has implications on product availability. This impact will be considered later in this document. The clearest example is in Germany that has a legal requirement requiring pharmacies to purchase a minimum of 5% of their supplies of medicines in parallel distributed product³⁷. Germany is the largest

³⁶ birgli research

³⁷ SGB V, § 129 Abs.1 No. 2 [3]). http://www.gesetze-im-internet.de/sgb_5/___129.html



pharmaceutical market with an ex-factory value in the area of €27 Billion³⁸. Simple mathematics would indicate that to meet the 5% figure Germany would need to parallel import in the area of €1.35 bln. EFPIA has estimated this figure to be closer to 11.8% or €3.0bn. With the EU parallel distribution market estimated at approximately €5bn³⁹, exports to Germany alone, sanctioned by the health ministry, would be somewhere between 30%-60% of the entire European parallel distribution market depending on which figures are used. Despite this, there are indications that parallel distribution figures in absolute terms are generally flat and declining in some markets as indicated later in this document.

Anecdotally, there also appear to be links between representatives of MAH in member states and parallel distributors during periods, when financial targets need to be achieved. With companies under such heavy pressure from price and budget reductions, that some turn to parallel distribution to support their bottom lines is understandable despite a clear industry position against the business.

4.2.4. Implementation of quotas and other artificial supply chain filters (as a partial reaction to parallel distribution)

With increasing differences in prices between markets, continued pressure on prices and reimbursement and other austerity measures, MAHs have implemented quota systems in most markets. The purpose of these quotas is to ensure products destined for one market remain in the market to meet local demand and to reduce parallel distribution.

These attempts are understandable due to the different levels of profitability, which a MAH has in each market. MAHs currently need to produce/supply according to local packaging and labelling requirements, and, should goods destined for one market be exported, there are potential difficulties to ensure products are available according to local regulations. There is thus also an interest from a manufacturing and supply chain perspective to reduce product flows out of the intended market.

Quotas are calculated based on a particular therapy's incidence in a market then allocated to the stakeholders involved. Virtually all pharmacies we discussed with, as well as the associations we have spoken to, refer to the difficulties quotas can cause due to their opaque application. Due to the implementation of quotas, pharmacies and patients often have difficulty sourcing products when they need them. Article 81 of Directive 2001/83 is often referred to by actors in the market and refer to the “.. limits of their responsibilities” in this area.⁴⁰

³⁸ Key Data 2012, EFPIA,
<http://www.efpia.eu/sites/www.efpia.eu/files/EFPIA%20Figures%202012%20Final.pdf>

³⁹ The implications of international reference pricing and parallel trade on social welfare and patient access: Final Report, Charles River Associates, September 2012

⁴⁰ birgli research



In direct discussions with pharmacies in all the markets reviewed, each has indicated that they have run out of quotas for a number of products at given points in time. Generally speaking the scenario is as follows: the pharmacy orders from their usual wholesaler, they are informed there is no quota left for them, the pharmacy contacts the manufacturer who, upon confirmation of a prescription behind the order, has the product delivered typically within 24-48 hours. Based on our intimate knowledge of the pharmaceutical supply chain, we can unequivocally state that in such cases the products are in the market. In that time frame they cannot be sourced from elsewhere and put into local country packs. From a pharmacist and patient perspective, there is a shortage since they did not get the product as quickly as they normally would; from a supply chain perspective a filter has been applied that has delayed product flowing to the customer.

Effectively what began as a tool to reduce parallel distribution has become a filter and effectively has created a class of shortages in its own right.

Although each market study shows the data sources of which products are in shortage, many of which are on quota, there is a general lack of quantitative figures to determine what the effect is on the perception & calculation of shortages in each market.

4.2.5. Increased risk of counterfeits and unscrupulous market behavior

A study in the United States raises another potential spectre linked to shortages. In markets where patients pay parts or all of the cost of medicines out of their own pocket there may be the temptation to seek less expensive alternatives on line. This risk is less likely in markets where the public health systems are still generally able to provide patients with the levels of healthcare they have received.

This study came to the conclusion that of the FDA listed shortage products, over 90% were quickly available on line on a majority of websites of which roughly 70% were not recommended by the National Association of Boards of Pharmacy (NABP).⁴¹

We list this study as a note of caution in particular for those markets where consumers cover a significant part of the cost out of pocket and the associated risk that they are driven to unsafe sources of product in attempts to acquire less costly access/channels to medicines.

4.3. Manufacturing & Supply Chain

4.3.1. Manufacturing

Many manufacturers have streamlined their production facilities and processes and acquired competitors in the process over the past years and continue to do so. As a result

⁴¹ Online Availability and Safety of Drugs in Shortage: A Descriptive Study of Internet Vendor Characteristics, 9 February 2012, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3374535/>



there are far fewer manufacturers and production facilities globally for most products. This applies as well to generic producers as it does to innovative ones.

A number of studies in the US have been conducted on shortages linked to manufacturing issues, with sobering results. In Europe we have had a few recent higher profile cases that have demonstrated this issue but we have found fewer reports reviewing this phenomenon in depth.

In the case of the US, of 168 products on the shortage lists due to manufacturing issues, 56 had no supplier, 23 only 2, and 7 none.⁴² Most of these products were generic injectable oncology products. Shortages in the UK recently occurred for isosorbide mononitrate (ISMN) due to safety concerns leading to shortages of the compound while alternative solutions were sought. The facility in question apparently produces a third of the world's supply of the product.⁴³

Another well-published case surrounding manufacturing shortages is linked to Ben Venue Laboratories in the United States. In this case production for a number of products including Caelyx, an oncology product, amongst others, were suspended by the EU due to GMP issues. Due to the importance of some of the products, "the UK's medicines regulatory agency (MHRA) on behalf of the European regulatory network issued a restricted GMP certificate to Ben Venue in order to stop the EU supply of non-essential medicines from Ben Venue, while allowing the continued supply of essential medicine." This one case demonstrates the potential risk of a limited number of production sites.

There is also the nature of the industry itself. Prices of medicines are generally fairly inelastic (not responsive) with limited opportunities for substitution for innovative products due to patents and for generics due to a declining manufacturing base. Furthermore, as a result of the heavy investment in plants and equipment to produce a product, any change in demand or requirements to establish new facilities means there is a certain lead time before a new facility can be put into place.⁴⁴

Regulations are quite clear regarding the communication of shortages due to manufacturing issues or policy (see regulation section). We do not however, have sufficient quantitative information to determine the real impact of manufacturing reasons on shortages. Based on our market reviews, however, there does seem to be a difference

⁴² Drug Shortages: A closer look at products, suppliers, and volume volatility, November 2011, IMS Institute for Healthcare Informatics, http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/Static%20Files/IIHI_Drug_Shortage_Media_ExecSumm.pdf

⁴³ Plant safety fears suspend angina med production, Julia Gregory, 19 Feb 2013, http://www.chemistanddruggist.co.uk/news-content/-/article_display_list/15308308/plant-safety-fears-suspend-angina-med-production

⁴⁴ ASPE.HHS.GOV Economic Analysis of the Causes of Drug Shortages, October 2011, <http://aspe.hhs.gov/sp/reports/2011/DrugShortages/ib.shtml>



in shortages between primary and secondary care, with shortages in secondary care linked to some emergency items for pain management, and others in oncology as mentioned.

4.3.2. Change in API legislation

Linked to the Falsified Medicines Directive (FMD), are regulations requiring that from 2 July 2013 all imported pharmaceutical ingredients manufactured in countries outside the EU must be accompanied by a written quality confirmation from the authorities of the exporting country. These must be provided per manufacturing site, per active ingredient, and effectively require that the standards of production and formulation are equivalent to those in force in the EU.⁴⁵ This directive is supposed to be enforced with inspections.

Since a number of major API supply markets, such as China, have not yet signed/joined the FMD agreement, there are concerns throughout the industry that shortages will result if import bans are put into effect. With these regulations coming into effect 2 July 2013, the concerns are becoming louder.

A “white list” of compliant countries is being maintained by the European Commission. As of the writing of this review, only Switzerland and Australia have been adopted with Israel, Singapore, Brazil, Japan, and the United States having made the request, please see (http://ec.europa.eu/health/human-use/quality/index_en.htm).

A full implementation by 2 July 2013 could result in significant disruptions for the importation of API's. Not only are there issues behind countries agreeing to conform to the terms behind it, enforcement measures, including on site inspections, are not yet in place. Costs for inspections alone are estimated at over €1 billion and funding for these has not yet been clearly defined to our knowledge.

4.3.3. Just-in-time - Supply chain considerations

Supply chains have become considerably compressed over the last years. Manufacturers who typically maintained up to 6 months of stock have reduced these quantities dramatically to reduce working capital, associated inventories, and therefore interest costs, ultimately boosting profit. This development is not unlike other industries where manufacturers have been using JIT (“Just-in-Time”) and related concepts to bring the amount of stock down as close as possible to market requirements.

In the case of generics, with inflexible pricing and innovative products with steep downward pressure on price, it is also important for manufacturers to streamline production processes and supply chains to reduce inventories and costs. Thus the amount of stock and flexibility in the supply chain will continue to decrease and be more susceptible to shocks of any kind.

⁴⁵ Key Deliverables of the Falsified Medicines Directive, 23 April 2013, Uday Shetty, <http://www.drugregulations.org/2013/04/key-deliverables-of-falsified-medicines.html>



Reducing shortages linked to manufacturing issues can be achieved by increasing capacity for example, but any approach to increase supply and production capacity would have an associated cost which no one is prepared to pay at this time.

Wholesalers have also been impacted by price and margin reductions over the past years. The effect has been for them to make their supply chains even more effective and streamlined than previously. With the number of products held by a wholesaler ranging from 15-20'000 in the UK to over 100'000 in Germany, stock needs to be managed very tightly to avoid significant inventories and associated financing charges.

Wholesalers have thus instituted inventory-holding policies that can be as short as 1-2 weeks for fast moving products depending on national legislation. For these products, any disruption in the supply chain from natural disasters (tsunamis and volcanoes) to strikes and other man-made issues, will have immediate ripple effects down the supply chain. These fast moving products are not always innovative new products, but also certain generics and generally lower priced products as well.

Pharmacies also have an interest to reduce stock holding. From a space perspective, it is not feasible to stock 15'000 or more products and as in pharmaceutical wholesaling, the top 1-2'000 products typically represent 80% of sales. Holding slow moving products represents a significant investment in space and financing. Thus pharmacies typically rely on wholesalers to quickly stock or restock them, a number of times a day per wholesaler in some cases. Thus, in many cases, pharmacies will actually not have the stock and will request their customers to come back later in the day or the following day.

In short, buffer stocks that were previously available to ensure supply in the market have been largely eliminated to improve general supply chain efficiency.

4.3.4. Channel Strategy including DTP

Manufacturers in have begun to implement DTP (Direct to Pharmacy) solutions in a number of markets in Europe. Wholesalers and parallel distributors often point to this structure as leading to inefficiencies and disruptions in the supply chain and negatively impacting Public Service Obligations (PSO) of wholesalers. In a number of markets wholesalers have PSOs whose requirements include having sufficient wide range of stock to serve an important percentage of products that a pharmacy needs to meet patient requirements.

DTP is a change in the distribution model that results in the current structure of PSO obligations no being applicable in their current form. They would require an updating of legislation accordingly to ensure that PSO to the patient is maintained. Direct and single channel solutions are, however, nothing new and have been very successful, transparent,

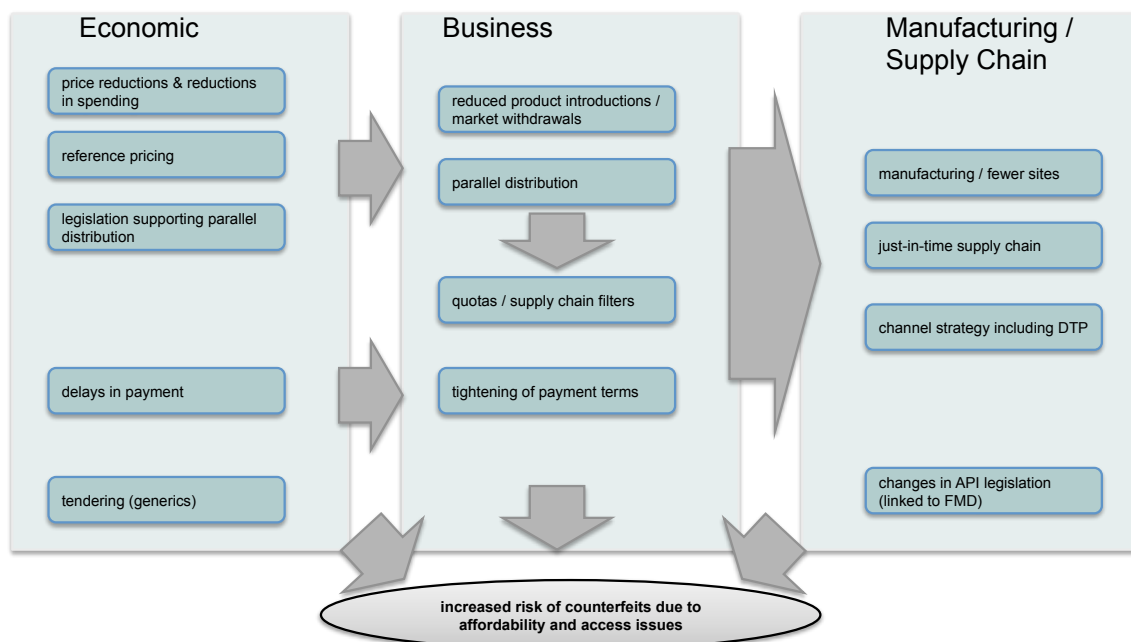


and cost effective in a number of markets world-wide including Scandinavia and South East Asia.⁴⁶

4.4. An illustrative summary of the causes of shortages

The previous discussion can be summarized with the following high level illustration.

An overview of the causes of shortages



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Figure 3: An overview of the causes of shortages

5. Regulation

The European commission has summarized a comprehensive list of European level directives covering the legal aspects of shortages. Although these are in place largely to cover shortages due to “manufacturing problems, poor quality, and lack of production capacity”, they could apply to shortages for other reasons as well.

⁴⁶ birgli research



5.1. Implications of existing European legislation

- The regulations listed below clearly state the obligations of MAHs to ensure markets are adequately supplied to cover the needs of the patient.
- They technically enforce MAHs obligations to notify the competent authority if the product is no longer on the market whether temporarily or permanently. Though the intent may have been to apply these for manufacturing or commercial issues, it could apply to shortages in general.
- If supplies are not sufficient, a member state could in principle, authorize sourcing and placement of a product without a marketing authorization on the market. In principle this could include (parallel) imports from jurisdictions even outside of Europe.
- These regulations could prevent or at least delay companies from withdrawing products from the market at least until solutions have been found (alternate products or suppliers)
- Force manufacturers (and wholesalers) to ensure that wholesalers & pharmacies have an adequate supply of product. This would have an impact on DTP solutions manufacturers are implementing in various markets.

Application of these regulations consistently and effectively could reduce shortages combined with better information and communication (see solutions/recommendations). These regulations are further supplemented with national regulations in a number of member states and will be covered in the discussions of the five markets we will look at in more detail.

These regulations are:

Table 7: Summary of relevant European directives ⁴⁷

Directive	Text / Summary
Article 81 of Directive 2001/83/EC on the obligation of continuous Supply:	<p>The holder of a marketing authorisation for a medicinal product and the distributors of the said medicinal product actually placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply Medicinal products so that the needs of patients in the Member State in question are covered.</p> <p>The arrangements for implementing this Article should, moreover, be justified on grounds of public health protection and be proportionate in relation to the objective of such protection, in compliance with the Treaty rules, particularly those concerning the free</p>

⁴⁷ Pharmaceutical Committee, 22 October 2012, 69th Meeting, Pharm 610, Agenda point 2.a), European Commission Health & Consumers Directorate General, http://ec.europa.eu/health/files/committee/69meeting/pharm610_shortages.pdf



Directive	Text / Summary
	movement of goods and competition.
<p>Article 126a of Directive 2001/83/EC on the use of medicinal products authorised in another Member States:</p>	<p>In the absence of a marketing authorisation or of a pending application for a medicinal product authorised in another Member State in accordance with this Directive, a Member State may for justified public health reasons authorise the placing on the market of the said medicinal product.</p>
<p>Article 5.1 of Directive 2001/83/EC on the use of unauthorised medicinal products:</p>	<p>A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility</p>
<p>Article 23a of Directive 2001/83/EC on the notification of cessation of marketing:</p>	<p>After a marketing authorisation has been granted, the holder of the authorisation shall inform the competent authority of the authorising Member State of the date of actual marketing of the medicinal product for human use in that Member State, taking into account the various presentations authorised.</p> <p>The holder shall also notify the competent authority if the product ceases to be placed on the market of the Member State, either temporarily or permanently. Such notification shall, otherwise than in exceptional circumstances, be made no less than 2 months before the interruption in the placing on the market of the product. Upon request by the competent authority, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the competent authority with all data relating to the volume of sales of the medicinal product, and any data in his possession relating to the volume of prescriptions.</p>
<p>Article 63.3 of Directive 2001/83/EC on labelling exceptions:</p>	<p>When the medicinal product is not intended to be delivered directly to the patient, or where there are severe problems in respect of the availability of the medicinal product, the competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars should appear on the</p>



Directive	Text / Summary
	<p>labeling and in the package leaflet. They may also grant a full or partial exemption to the obligation that the labeling and the package leaflet must be in the official language or languages of the Member State in which the medicinal product is placed on the market.</p>
<p>Article 20 of Regulation (EC) No 726/2004 on referral for medicinal products that have been authorised via the centralised procedure</p>	<ol style="list-style-type: none"> 1. Where the supervisory authorities or the competent authorities of any other Member State are of the opinion that the manufacturer or importer established within the Community territory is no longer fulfilling the obligations laid down in Title IV of Directive 2001/83/EC, they shall forthwith inform the Committee for Medicinal Products for Human Use and the Commission [...]. 2. The Commission shall request the opinion of the Agency [...] 3. Following an opinion by the Agency, the Commission shall adopt the necessary provisional measures, which shall be applied immediately. [...]
<p>Article 31 of Directive 2001/83/EC on EU interest referral for medicinal products that have been authorised via the decentralised procedure or mutual recognition procedure</p>	<p>The Member States, the Commission, the applicant or the marketing authorisation holder shall, in specific cases where the interests of the Union are involved, refer the matter to the Committee for application of the procedure laid down in Articles 32, 33 and 34 before any decision is reached on an application for a marketing authorisation or on the suspension or revocation of a marketing authorisation, or on any other variation of the marketing authorisation which appears necessary. [...]"</p>

Additional articles would include:

Directive	Text / Summary
<p>Article 1 (18) of Directive 2001/83/EC as amended 2004/27/EC</p>	<p>The obligation placed on wholesalers to guarantee permanently an adequate range of medicinal products to meet the requirements of a specific geographical area and to deliver the supplies requested within a very short time over the whole of the area in question.</p>



5.2. Summary - Other markets

5.2.1. Germany^{48,49}

Germany has fairly comprehensive regulations surrounding the availability of medicines on the market. With the exception of periodic shortages of generics due to an aggressive tendering scheme, German pharmacies have not registered significant shortages.⁵⁰ We did not review secondary care.

A few key pieces of legislation follow. The legislation applies to manufacturers, wholesalers, and pharmacies. Effectively they ensure enough stock in the market that could cover short-term shortages.

5.2.1.1. §52b of the 15th amendment to the AMG

- Requires manufacturers to "ensure an adequate and continuous supply" of medicines to wholesalers to meet at least an average two-week demand and for stock.
- Wholesalers in turn are obliged to supply every pharmacy with which they have a business relationship with a full assortment so as to satisfy the needs of patients on working days within an appropriate period of time.
 - the above only applies to full-line wholesalers stocking all 30'000 or so pharmacy only SKU's
- Manufacturers remain free to choose which wholesalers they have dealings with and how based on the wholesaler's need to carry out the PSO for its local market
- Need can be determined for existing products by using market data to show demand in the corresponding month the previous year, plus a reasonable safety margin.
- After the launch of a new medicine, a need-based assessment can be made after a specified period, if necessary.
- In case of a doubt, a full line wholesaler who claims a need-based supply, must demonstrate that need.
- Other forms of commerce, especially exporting or parallel distribution within the EU, do not constitute need.
- Certain unspecified circumstances or certain product types (radiopharmaceuticals, narcotics) may preclude distribution through wholesalers

5.2.1.2. §15 Apothekenbetriebsordnung

This regulation pertains to pharmacies and seeks to ensure that pharmacies hold sufficient stock to cover average demand over two weeks. There is also an appendix that lists certain medicines that must be stocked or available in a very "short" period of time.

5.2.1.3. Germany - 5% requirement

As mentioned earlier, Germany also has a clear regulation requiring pharmacies source at least 5% of their requirements via parallel distribution. One can argue that parallel distribution helps ensure there are fewer shortages in Germany.

⁴⁸ SGB V, § 129 Abs.1 No. 2 [3]). http://www.gesetze-im-internet.de/sgb_5/_129.html

⁴⁹ birgli research

⁵⁰ Medicines' shortages in the EU (PGEU Fact Sheet), 4 June 2012, Ref: 12.04.06E 005FS



6. Country Analysis

6.1. Benchmark/Comparator

6.1.1. USA

The United States is an interesting benchmark for Europe from a number of perspectives:

- As a large homogenous market with somewhat better quantitative data on shortages, there are potential parallels that can be applied to Europe as a whole (Europe as a whole is just over 60% the size of the US market).
- Parallel distribution is not permitted, shortages are thus clearly linked to other factors.

6.1.1.1. Shortages in the US^{51,52}

- In 2011 there were 267 recorded product shortages in the US up from 211 in 2010. 300 are currently in short supply (as of April 2013).
- The cost estimate just to manage shortages run as high as US\$400 million (€310 million).
- Over 60% of hospitals report that they rarely receive advance warning of shortages from manufacturers, wholesalers, distributors, group purchasing organizations (GPOs), or the FDA.
- 95% & 91% of hospitals respectively experienced shortages in Surgery Anesthesia and Emergency Care respectively, 66% in hospitals.
- The drug shortage problem especially affects generic injectable drugs(80%), of the total generic market, half are on the shortage list.
- Most of the drugs are supplied by only one or two companies.

Out of 168 products on the shortage list in October 2011, the top three reasons for shortages in the US are due to:

- | | |
|--------------------------|-----|
| • Manufacturing Issues | 22% |
| • Discontinued/suspended | 20% |
| • Increased demand | 15% |

Thus fully 57% of the shortages are not linked to legislation, austerity, and parallel distribution. From our perspective, elements of the same issues most likely exist in Europe as well but have not been quantified as they have in the US.

In our estimation the cost of managing shortages in the EU are probably of a similar order if not higher due to the current economic climate and the more heterogeneous environment of Europe.

⁵¹ ISMP Webinar “Taking Charge when Drug Shortages Arise: A Model for Decision Making and Actions” 14 February 2013

⁵² Drug shortages persist despite federal efforts to stop them, Number of new shortages has dropped, 15 May 2013. The Daily Briefing, The Advisory Board Company, <http://www.advisory.com/Daily-Briefing/2013/05/15/Drug-shortages-persist-despite-federal-efforts-to-stop-them>



A recent study shows that 83% of US oncologists have faced cancer drug shortages which have affected patients treatment. They have indicated that generic drugs are often the most difficult to obtain due, in part, to manufacturing problems, but also to “decisions by drug makers to deprioritize production because of slim margins on generics”.⁵³

This reflects our earlier discussion on the economics of ensuring product availability when under significant margin / pricing pressure and serves as a cautionary tale for Europe where similar cases appear to be occurring.

6.1.1.2. Legislation in the US addressing shortages

The FDA issued a revision to the 21 CFR Part 314 regulation around the Post Marketing Requirements in response to increases in shortages and their effect on patient outcomes.^{54,55}

President Obama furthermore issued Executive Order 13588 directing the FDA to “take steps that will help to prevent and reduce current and future disruptions in the supply of lifesaving medicines.” This is a clear directive from the top to address the problem.

The provisions set in place more stringent and clearly defined requirements than those we have reviewed for the EU.

These include:

Require manufacturers who are the sole manufacturers of certain drug products to notify FDA at least 6 months before discontinuance of manufacture of the products

“discontinuance” means “any interruption of manufacturing of a drug product described in paragraph (b)(3)(iii)(a) for sale in the United States that could lead to a potential disruption in supply of the drug product, whether the interruption is intended to be temporary or permanent.’

The rules go beyond sole manufacturers and include many circumstances that can lead to a “discontinuance”.

With such stringent reporting requirements, the causes and effects of shortages are clearer in the United States though the verdict is still out on whether shortages are reducing because of them.

⁵³ Cancer drug shortages hit 83% of US oncologists: study, 4 June 2013, Lynne Taylor, PharmaTimes, www.pharmatimes.com/mobile/13-06-04/cancer_drug_shortages_hit_83_of_us_oncologists_study.aspx?r=1

⁵⁴ ASPE.HHS.GOV Economic Analysis of the Causes of Drug Shortages, October 2011, <http://aspe.hhs.gov/sp/reports/2011/DrugShortages/ib.shtml>

⁵⁵ Department of Health & Human Services (HHS) - 21 CFR Part 34 [Docket No. FDA-2011-N-0898], Federal Register / Vol. 76, n0. 243/ 19 December 2011



6.2. United Kingdom (UK)

Shortages have been in the press with a number of studies and reports being issued with alarming frequency on the topic.

6.2.1. Available list of shortages

Shortages are today primarily tracked by the PSNC at:

www.psn.org.uk/pages/problem_medicines_list.html for branded products.

This list tracks all medicines reported directly to PSNC as in short supply by pharmacists and is separate from products listed as MCS (Manufacturer Cannot Supply) internally by wholesalers and other suppliers. Generally, it is believed to correlate strongly with products that are being exported from the UK, which may also be part of quota/DTP schemes.

A second list http://www.psn.org.uk/pages/generic_shortages.html for generic products covers shortages of generic products that cannot be obtained at or below the reimbursement (Drug Tariff) price and are subject to the NCSO (No Cheaper Stock Obtainable) Scheme. Although generics are less subject to parallel distribution, shortages and related opportunistic trading within the UK is surfacing.

The two lists are used as a basis from which the Department of Health (DOH) tracks market shortages. The DOH apparently does track the market on a wider basis but this information, to our knowledge, is not publicly available. Manufacturers are expected to keep the DOH formally advised of any issues which relate to product shortage and plans for their resolution.

From the perspective of the PSNC, shortages in generics are on the rise as well. Generics are generally not subject to parallel distribution, therefore there are other issues affecting supply as the experience in the US points out.

6.2.2. Agencies

In the UK, the DOH oversees policy and operation of national medicines expenditure in both the Primary (community) and Secondary (Hospital/Institutional) sectors. There is however an important distinction to supply - primary care operates chiefly through independent contractors (pharmacies) whilst secondary care operates in the main via directly reporting organisations (e.g. NHS Trust Hospitals) and public sector employees. This leads to two distinct medicines supply chains, markets and cultures.

As an Agency of the DOH, the Medicines and Healthcare Products Regulatory Agency (MHRA) can affect the availability of product primarily through:

- Expediting any manufacturing, quality or licensing bottlenecks including supply of alternatives
- Granting Marketing Authorisations to imported products



- Granting and policing Wholesale Dealers Licenses which govern the terms and conditions under which Prescription Only Medicines (POM) may be supplied / traded including collation for (parallel) export.

Secondary Care has developed a successful formulary and contracting model (ie tendering model). By means of a pharmacy driven model to contain the escalating drugs bill within NHS Hospitals the Department of Health, through its Commercial Medicines Unit (CMU), now plays a pivotal role together with sister bodies in Scotland, Wales and Northern Ireland. The focus of the work of the CMU is on strategic supply management and procurement of medicines for use in secondary care. The team works in partnership with hospital pharmaceutical procurement colleagues across the NHS in England. It is important to note that the CMU has very limited oversight over primary care (pharmacies) shortages.

Relevant facilitators include teams of category specialists, National Pharmaceutical Supply Group (NPSG) Pharmaceutical Market Supply Group (PMSG) which contribute to policy and operating procedures whilst ensuring communication between the DH, regions, consortia and hospital end-users. A high clinical pharmacy input is critical in this respect.

Their objectives are to ensure a stable supply of drugs and to maintain, develop and realise the benefits of competition. It therefore plays a prime role in anticipating, mitigating and managing shortages.

Despite these measures, shortages can and do occur, but the same operating procedures can be deployed as they are for disaster and pandemic planning. Communication and information is broadly in place to aid management - for example, stock can be moved to the place of greatest clinical need.

6.2.3. Definition/understanding of shortages by stakeholders

Based on discussions with pharmacists and articles to this effect in the Chemist & Druggist website, we find that in most cases when (community) pharmacies are informed by wholesalers that they are not in stock or out of quota, they can get the product within 24-48 hours “directly” from the manufacture (usually with proof of a prescription). Although a pharmacist and patient may consider this a “shortage”, as mentioned earlier; based on our knowledge of the supply chain, these products are actually already in the market. Through the application of a filter with quotas or supply chain issues with the wholesalers, there is a delay getting the product to the point of dispensing.

In cases such as this, we would argue that the product is not in shortage. There is, however, a considerable amount of time and effort lost to source product. These delays have other impacts as will be discussed shortly.

Regardless of the definition, there is very limited published quantitative data on shortages in the UK.



In a study of around 500'000 incidents (ref 6.2.5.2 below), the National Patient Safety Agency identified 'omitted and delayed' at 16% as the largest category. Unfortunately, the study does not distinguish between 'shortages' defined as distributors or manufacturers failing to supply on time (i.e. external supply chain cause) against a timely, valid pharmacy order (internal supply chain cause).

6.2.4. Primary causes based on analysis by stakeholders & interviews

Through our surveys two primary causes were listed for shortages.

6.2.4.1. *Manufacturers*

Manufacturers together with the APPG⁵⁶ place the cause of the problem more or less directly on parallel distribution (causing them to put into place a quota system).

6.2.4.1. *Pharmacies, Hospitals, Wholesalers, and Prescribing Physicians*

The remaining stakeholders we spoke to, however, anecdotally listed quotas as being a major source of concern followed by perceived disruptions to the supply chain with the implementation of DTP. Manufacturing problems, for innovative products, were not viewed as being too significant.

In the case of generics, however, manufacturing issues were viewed as the primary concern. It would be interesting to compare statistics with the US in this area.

In addition to pharmacies, hospital pharmacies and stores also need have wholesale dealers licences as a matter of course. Hospitals report regular canvassing by traders and there are sporadic suggestions that discounted product sold into secondary care has leaks into retail pharmacy or has been exported. The scale is unclear but following a review, the Chemist & Druggist reported that 126 of England's 166 hospital trusts had not exported any medicines for profit between July 14, 2009 and June 17, 2011. The remaining 40 trusts did not respond to C+D's request.

No quantitative data was available to determine an actual breakdown of the causes.

6.2.5. Current consequences of shortages

6.2.5.1. *Primary Care*

The Chemist & Druggist recently conducted a survey on the burden of shortages for pharmacies in the UK. The following were some of the results:

- Pharmacists spent an average of 15 hours a month following up with wholesalers and manufacturers on shortages

⁵⁶ APPG Pharmacy - Report of Inquiry Into NHS Medicines Shortages, 15 May 2012, <http://www.appg.org.uk/APPG%20Pharmacy%20-%20Report%20of%20Inquiry%20Into%20NHS%20Medicines%20Shortages.pdf>



- This lost time is lost revenue for other services and time that can be spent with patients. It is estimated that this resulted in 2.5 million lost hours per annum across the countries 13'700 pharmacies.
- 35% received their products in 1-2 days, 40% typically within 3 days for emergency delivery with the rest beyond this period
 - The implication here is that for more than 75% of the time, the product is in the UK with a delay in reaching the pharmacy

6.2.5.2. *Secondary Care*

Besides primary care, there is growing concern in secondary care, with order lines not delivered on-time (or at all) having probably doubled in the last decade with an acceleration post 2010. Today a hospital may have up to 400 ordered lines exceeding expected delivery times at any one time. Although up to 50% may be temporarily MCS (manufacturer cannot supply), only a few of these will be serious stock-outs or critical shortages. Despite this, the handling of these has been estimated to cost the NHS between £3-5m annually in staff time. Although there is little overlap with PSNC listed products, medicines shortages are a significant and growing concern in secondary care.⁵⁷

Between 2005-2010, another arm of the DOH, NHS NPSA (National Patient Safety Agency- now within the NHS Commissioning Board) reviewed the reasons behind 526'000 medication incidents. 75% were reported from acute general hospitals against 8.5% from primary care. In total 16% reported actual patient harm.⁵⁸

6.2.5.3. *Patients*

As will be the case in other markets, patients are affected by shortages, delays, and access to medications. In the case of the UK all three are concerns but this report reviews only the first two.

The concern of patients surrounds the availability of medicines for chronic conditions. The image of the healthcare system also suffers when product is not available and patients also have the added burden of returning to the pharmacy for product or possible substitution.

Based on a C&D survey of more than 370 respondents, 16 per cent said the health of more than 20 of their patients had suffered because of shortages in 2012, with 6 per cent of respondents putting the toll at more than 30 patients. Forty-two per cent of respondents said they had to turn away up to five patients a month because they could not obtain their

⁵⁷ UK research by birgli

1. ⁵⁸

Cousins, D. H., Gerrett, D. and Warner, B. (2012), A review of medication incidents reported to the National Reporting and Learning System in England and Wales over 6 years (2005-2010). *British Journal of Clinical Pharmacology*, 74: 597-604. doi: 10.1111/j.1365-2125.2011.04166.x



medication, and 27 per cent said they had to contact GPs more than 30 times last year to ask them to change prescriptions.⁵⁹

Though this survey did not show the impact on patient outcomes, it does show that there is a certain level of risk on the market.

6.2.6. Current market specific solutions/suggestions

Various bodies have recommended many solutions and approaches. In general these will overlap country by country.

One creative suggestion we have seen in the UK came from a parallel distributor who has offered to return stocks to pharmacies (who have sold to the company) at the same price sold (no gain) should they have a shortage. Out of roughly 500 pharmacies, all holding wholesaler licences, from whom this trader sources, none have yet come back with a request for a “reverse” importation.

Another suggestion, via an MP, would be to use VAT returns to track movements of products declared or noted to be in shortage in the market. How this would operate in practice is not clear.

6.2.7. Regulations in place on shortages

The UK has a number of regulations in place beyond those from the EMA. The Department of Health has issued “Shortages and Supply Chain Obligations” in January 2013 updating those issued in 2009.⁶⁰ This document refers to the Human Medicines Regulations 2012 (SI 2012/1916).

It covers the key stakeholders in the supply chain namely Manufacturers, Wholesalers (from a sourcing and supplying perspective), NHS Trusts (hospitals), Registered Pharmacies, and dispensing doctors.

In its conclusions, it asks all parties to consider the consequences on the patient as well as being “aware of the consequences of exporting medicines for the supply of medicines to UK patients.”

The ABPI (The Association of the British Pharmaceutical Industry) and the DOH in 2007 also issued joint best practice guidelines on “Notification and management of medicines and

⁵⁹ Pharmacists spend two days a month chasing out-of-stock drugs, Gemma Collins, 10 April 2014, Chemist + Druggist.co.uk, http://www.chemistanddruggist.co.uk/news-content/-/article_display_list/15512433/pharmacists-spend-two-days-a-month-chasing-out-of-stock-drugs

⁶⁰ Trading Medicines for Human Use: Shortages and Supply Chain Obligations, DH Gateway reference number 18605, January 2013, Department of Health (UK)



shortages”. Though these are voluntary, they do refer to the statutory requirements under EC Directive 2001/83/EC mentioned earlier.

Though there are general regulations in place, there are quite a few voluntary components that perhaps need to be reviewed should the issue of shortages continue to worsen.

6.3. France⁶¹

6.3.1. Available list of shortages

A current list of shortages is available on the website managed by the ANSM:

<http://ansm.sante.fr/S-informer/Informations-de-securite-Ruptures-de-stock-et-arrets-de-commercialisation-des-medicaments>

6.3.1.1. Agencies

The ANSM (Agence Nationale de Sécurité du Medicament et des produits de santé) is the body concerned with shortages in France.

6.3.2. Definition/understanding of shortages by stakeholders

The definition of shortages in France has been widened as can be seen in the section on regulations. All stakeholders are technically involved and have a fairly clearly defined responsibility.

In France a shortage is defined as when a pharmacist has not been able to receive the product they have ordered within 72 hours.

6.3.3. Primary causes based on analysis by stakeholders & interviews

Our analysis of the anecdotal causes of shortages in France has not led to any significant surprises.

6.3.3.1. Manufacturers

Manufacturers have put into place quota systems as in other markets to ensure product supply and reduce parallel exports. Wholesalers, distributors and pharmacies contest this activity as they do in other markets.

6.3.3.2. Wholesalers

Our discussions with the wholesalers association pointed to market withdrawals, API shortages, quotas, and low stock levels in pharmacies and distribution centres. They claim that parallel exports are not, in contrast to manufacturers, a major cause of shortages in the market. They pointed out that they do not export anti-retrovirals, for example (we were not able to independently confirm these statements).

⁶¹ France research by birgli



In general wholesalers are not satisfied with the current approach to regulation, as they are seemingly excluded from emergency supply measures, despite an efficient distribution network that is already in place.

6.3.3.3. Hospitals

The concerns of hospitals are primarily with market withdrawals and shortages of API's. Since hospitals source directly from manufacturers in most cases in France and have more centralized logistics structures, they are apparently able to move product between units which is more complicated than between community pharmacies.

Hospitals are also better able to contact the ANSM to get temporary authorization to import product if there is a shortage on the market.

6.3.3.4. Pharmacies

Pharmacies in France in general appear to be well informed about shortages, though perhaps not their causes. Being at the end of the supply chain, however, they face similar shortage related issues as other pharmacies in other markets

6.3.3.5. General Comments

As in other markets shortages in France range from manufacturing issues, quota systems, parallel exports, just-in-time related challenges, increases in demand (measles outbreak), and others as already described.

One issue did stand out, however. In 2012 a price reduction on generics was announced. This led to a 30% growth in demand prior to the price reduction, which in turn led to a number of shortages throughout the market.

6.3.4. Current consequences of shortages

Our review has shown that shortages at pharmacy level can reach up to 15% of orders placed. There are, however no precise and official statistics on the causes shortages in France, though anecdotal data abounds.

The ANSM is however collecting data on shortages based on the legislation you can see below. In March the shortage situation in France was summarized as follows:

Table 8: Shortage situation in France

In Shortage	At Risk of Shortage	Market withdrawal	Reset to available status
42	19	24	36
34.71%	15.70%	19.84%	29.75%



6.3.5. Current market specific solutions

6.3.5.1. Centrally driven solutions

The ANSM is apparently in the process of conducting an exhaustive review of shortages. We asked for the status and were informed that a report will be issued after a one year data collection period which ends in October 2013.

We expect that France, upon completion of this consultation period, will undertake an extensive legislation driven change to reduce and manage shortages in the country.

In the interim, regulation is improving transparency and the requirement of emergency call centres is putting pressure on manufacturers to increase supply or balance increased supply vs. the cost of managing such systems.

6.3.5.2. Creative approaches

One leading wholesaler has set-up a central warehouse for slow moving product. This will help ensure adequate stock in the right place for a very large number of SKU's.

A number of pharmacies in the south have combined their reserve stock, much like a group purchasing organisation (GPO), which is sheltering them from more frequent stock-outs. There is a concern however, that as more of these groups take similar action, there may be periodic shortages due to increased bulk purchases by these groups (possibly with special payment terms with MAHs).

6.3.5.3. Association driven proposals

A number of association driven initiatives are also apparently in discussion including:

- All hospital tenders should include a mandatory analysis of the risk of shortage and alternative solutions in the event of them.
- Banning of the exportation of medicines without therapeutic equivalents.
- Creation of a security buffer stock for sensitive medicines.
- Full transparency on Importation/exportation of product and quota systems currently in place.
- More involvement of the authorities to define a national policy for shortage management

6.3.6. Regulations in place on shortages

6.3.6.1. Article R 5115-13 Code de la Santé Publique requires every wholesaler to:

- Communicate to the national Medicines Agency (ANSM) details of the territory the company covers (every district containing one or more pharmacies where sales are normally made by the wholesaler must be included).
- Hold in stock at least 90% of all medicines used in France whether reimbursed or not.
- Have a 2 week supply capacity for their usual customers
- Supply the orders of any pharmacy within its territory. Pharmacies outside the territory can (and on decision of the authorities must) be supplied under exceptional circumstances
- Be able to deliver within 24 hours at a maximum.
- Inform the authorities as soon as there is a reduction in stockholding
- When no other source of supply is available, the DG of the ANSM can, as an exception, require a wholesaler to deliver to a pharmacy outside its normal territory



The above comprises the PSO of wholesalers in France

6.3.6.2. Decret 2012-1096 2012/09/28

This regulation was put into place at the end of 2012 to specifically address shortages. In short it requires the following:

Table 9: Decret 2012-1096 2012/09/28 (decree in France)

Item	Summary
Raw Material	Any company involved in production, importation, distribution of raw material used for pharmaceutical manufacturing, must declare their identity to ANSM
Territory covered	All pharmaceutical distributors must define which territories they are covering
Medicines having “major therapeutic importance”	Each product considered having being of “major therapeutic importance” is covered by the alert procedure of the regulation. These products are considered as critical for patient outcomes. The ANSM has put together this list
Alert & Information	<p>The ANSM must be informed by MAH / Manufacturers as soon as they expect/suspect a shortage to arrive. There are 4 clearly defined cases: Batch withdrawal, shortage, risk of shortage, market withdrawal (with sufficient time to set-up alternatives)</p> <p>The alerts need to be sent to all stakeholders in the supply chain including wholesalers, hospitals, & pharmacies.</p>
Emergency Call Centres	MAH / manufacturers need to set-up call centres providers can access when a shortage occurs and to set-up direct supply channels where appropriate

The above guidelines parallel those present in the United States. There is a clear target to achieve transparency on shortages and the causes behind them to set the stage for effectively dealing with them.

These complement the PSO regulations covered earlier.



6.4. Greece⁶²

Greece presents one of the more complex cases in Europe today. It is a market that has been most significantly hit by the financial crisis and austerity programmes. Some of the impact was covered in our previous discussion on Economic, Business & Supply Chain causes for shortages.

In the case of Greece, hundreds of drugs are in short supply ranging from treatments for arthritis, hepatitis C, antibiotics, cardiovascular diseases, cholesterol-lowering agents, antipsychotics, anaesthetics, various oncological medicines, to immune-modulators, and virtually all others.

6.4.1. Available list of shortages

Current shortages are available on the site of the National Organization for Medicines (EOF <http://www.eof.gr/web/guest/home>)

6.4.2. Definition/understanding of shortages by stakeholders

To create some level of context, it should be noted that between the years 2000 and 2009, pharmaceutical sales in the market increased by 225% (including parallel exports). Public spending during this period increased by over 117%, from €2.4 billion in 2004 to €5.2 billion in 2009, more than double.

It is widely recognized now that the bulk of this increase in consumption was due to

- Over-prescribing within public social security system and
- Slow adaptation of the Government to review prices for off-patent products.

With the onset of the financial crisis there have been significant decreases of 29,4 % in total sales and 45,5 % in the public spending for reimbursed medicines.

The Second Economic Adjustment Programme for Greece (Second review - May 2013)⁶³ measures aim at achieving savings in the purchasing (accrual basis) of outpatient medicines to reach spending of about EUR 2.440 billion and inpatient to reach spending of about EUR 0.66 billion in 2013 (accrual basis). The goal is to bring public spending on outpatient pharmaceuticals to about 1% of GDP i.e. around EUR 2 billion euro (in line with the EU average) in 2014. Total (outpatient plus inpatient) public expenditure on pharmaceuticals should be no more than 1.5 per cent in 2013 and 1.3 per cent in 2014.

⁶² Greece research by birgli

⁶³ The Second Economic Adjustment Programme for Greece Second Review - May 2013, Occasional Papers 148, May 2013, European Commission, ISSN 1725-3209

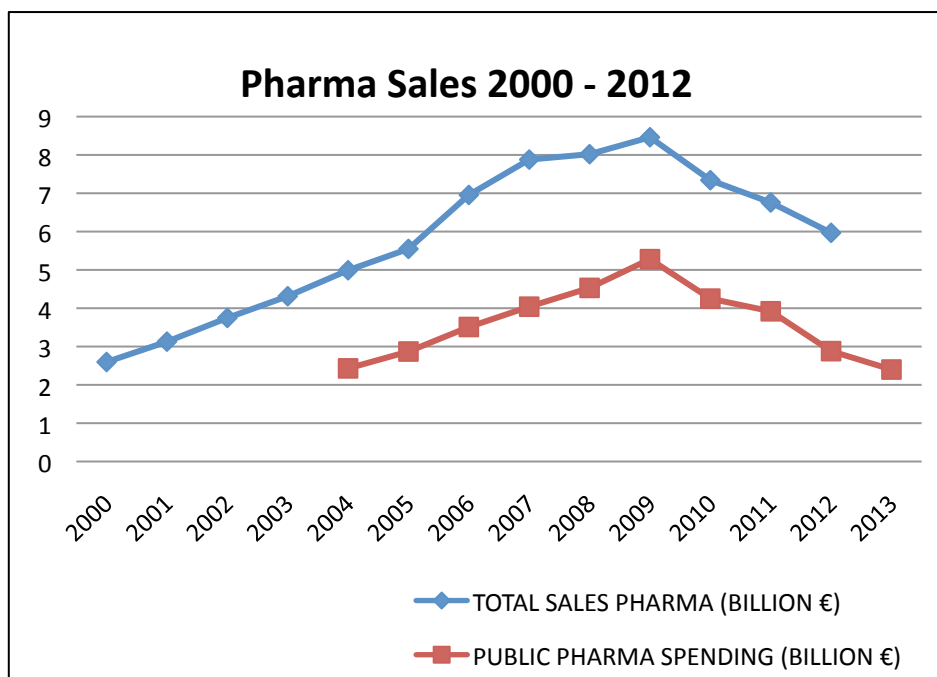


Figure 5: Pharmaceutical Sales in Greece⁶⁴

Public spending in 2013 is expected to be below the levels of 2004.

6.4.3. Primary causes based on analysis by stakeholders & interviews

Parallel distribution, in the case of Greece parallel exports, are often named as the main cause for shortages in medicines for which there is no possibility for substitution.

Official data for the legally performed parallel exports have only been collated since 2009 by the EOF. According to the export data announced by licensed wholesalers, there was a gradual reduction in values between 2009 and 2012 from €650 million to €420 million (-35%).

In 2012, although there was a significant change in the product mix of exported medicines, the trend continued.

⁶⁴ CEO IMS Health Greece

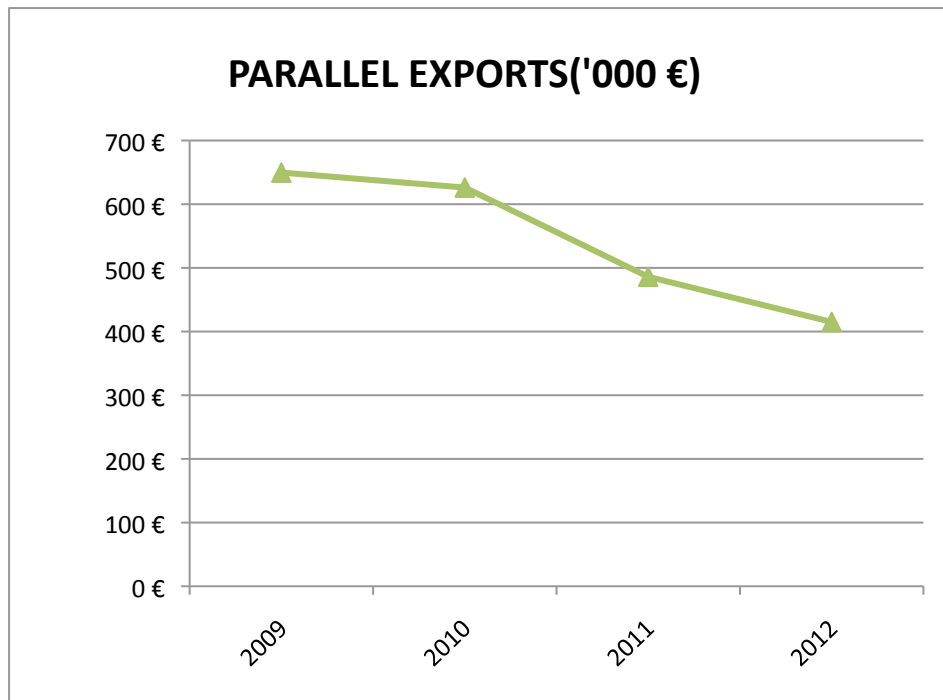


Figure 6: Parallel exports from Greece

As expensive therapies are dispensed either through the pharmacies of public hospitals or through the pharmacies owned by the National Organization for Healthcare Provision (EOPYY), there is an access barrier for exporters to source expensive medicines.

The cuts in prices (for innovative or generic products) have made Greece a prime location for wholesalers to buy cheap products for re-export. According to the statements of wholesalers, there is a change in the lists of exported medicines: cheaper brands but in higher quantities plus the appearance of illegal exports may in fact keep the overall turnover of parallel exports constant despite the reduced official figures of EOF.

Despite the price differences, cuts in prices and austerity have resulted in pharmacies & hospitals not being able to stock products due to liquidity issues. Most of those interviewed have pointed to the difficult financial situation/liquidity and general market access issues as being the leading cause for shortages as the following survey indicates.



Table 10: Survey summary - Greece

Statements made by stakeholders	PHARMA COMPANIES	WHOLE-SALERS	PHARMA-CISTS	HOSPITALS	DOCTORS	AUTHORITIES	MARKET ANALYSTS
Multinational pharmaceutical companies decreasing imports due to the financial crisis and to hospital debts, and demand cash payments from wholesalers and hospitals.	2	5	5	5	4	4	5
Low prices for pharmaceutical products making products (on-patent and off-patent) more attractive for legal re-exports.	5	3	4	3	4	3	5
Multinational pharmaceutical companies withdrawing products due to their low price and the consecutive damage caused in other European countries (reference pricing system).	1	4	4	4	5	5	4
According to the conditions set by the country's lenders, the pharmaceutical expenditure [as a part of the overall health expenditure] went down from € 5,6 billion (4009) to € 4,8 billion in 2014 and has to reach € 4,1 billion in 4014. This measure is not equipodenrous.	5	3	3	2	5	3	4
Social Security debts to Pharmacies for reimbursed drugs cause permanent cash flow problems to pharmacists who are small independent professional (chains not allowed in Greece).	1	3	5	3	4	2	5
Repetitive erroneous application of the pricing system by the Government to not allow patients to gain access to new medicines.	5	2	2	2	5	1	4
Low substitution possibilities due to low market share of Generics in the total pharmaceutical spending in the pharmacies (reimbursed by the social security) and in hospitals.	2	3	3	4	1	3	4
Growing illegal parallel exports organized by newly established wholesalers and not controlled by the authorities.	3	2	2	1	2	5	2
Pharmacists co-operate with wholesalers by reselling export oriented drugs due to their cash flow problems.	4	1	1	1	1	5	3
Minimum quota for the compulsory coverage of the demand using re-imported products in countries with higher prices (e.g. Germany).	1	2	1	1	1	2	3

6.4.3.1. Survey summary

Based on the answers we received in Greece, we have been able to weight the anecdotal causes of shortages with some key economic indicators. The following table includes ten statements made by the persons who answered to the questionnaire either during an interview or in written form (in Greek) via e-mail. The point of view of some interest groups has become common knowledge because they regularly make it public in TV interviews, newspapers and professional congresses.

According to the significance attributed to the various causes for shortages, they have been assigned a weighting ranging from 5 (very important) to 1 (not so important).

The first four statements total approximately 50% of the 217 points possible. From this analysis the market views on the chain of events causing shortages in Greece are:

- The dramatic increase in pharmaceutical expenditure on pharmaceuticals (2009: €5.2 billion)
- Crisis measures to bring this figure down to 2,1 billion € until 2014 (memorandum of understanding between Greece and its lenders).
- Consecutive reductions of prices for all Rx products.



- The inability of the Government to pay for the hospital pharmaceuticals. On December 31, 2012 the total unpaid invoices issued between 01.01.2010 and 30.06.2012 hit €1.38 billion.
- The inability of the National Organization for Health Care Provision (EOPYY) to pay pharmacies (open items from Nov 2012).
- Pharmaceutical companies, following instructions from their respective headquarters were forced to take measures in order to safeguard cash flow, receivables, and to better control parallel exports

In our view, this is a near “perfect storm” to cause shortages.

6.4.4. Market notification process

Shortages are reported to the National Organization for Medicines (EOF) through the various local Associations of Pharmacists as well as through the hospital’s pharmacies in written form.

Citizens can also report shortages directly to EOF though they usually prefer to inform the media hoping for assistance in their effort to find the needed medicine. Some of the articles we have seen are indeed tales of desperation.

More recently, EOF has offered the possibility for registered users to directly report any shortage they become aware of. There are as of yet no official statistics from this site.

6.4.5. Current consequences of shortages

The consequences of shortages on patients is the most evident in Greece. Patients previously receiving medicines in some cases simply no longer get it from their original public source. Cash has become the primary currency for medicines and shortages in the markets, even for those with the ability to pay directly, and has lead many to seek medicines outside the country.

Some of these cases are particularly heart breaking and difficult to read about particularly since there are no ready and quick solutions.

6.4.6. Current market specific solution

If shortages are judged to become a risk for the public health, the EOF will apply the following measures:

- A temporarily limited ban of parallel exports for medicines with short supply.
- Fines on the MAHs for not covering the domestic market with a 3-months’ stock, as required by law.

6.5. Poland⁶⁵

Poland falls clearly into the classification of a “low priced” markets with average generic prices typically 43% lower and 59% lower for innovative products than the rest of Europe.⁶⁶

⁶⁵ Poland research by birgli



Despite this, Poland has recently pushed through a reimbursement act whose target is to increase the availability of reimbursed drugs for the patient, reduce the retail price of medicine, reduce the level of co-payment, and reduce the cost of reimbursement.

6.5.1. Available list of shortages

There are a number of sites which track shortages. One is maintained by the Ministry of Health (MOH), and covers products that are mainly affected by manufacturing issues, withdrawals, and other issues. It can be found at <http://www.gif.gov.pl/?aid=205>.

Another is maintained by the Regional Pharmaceutical Chamber of Poznan, which consists of voluntary reporting by member pharmacies, similar to that of the PSNC in the UK. They can be contacted directly for more information.

6.5.2. Primary causes based on analysis by stakeholders & interviews

Five primary causes of shortages arose during our discussions with various stakeholders and market research. Please note that these are not in any particular order:

6.5.2.1. *The Reimbursement Act*

From a government perspective, the new Reimbursement Act has been successful. Costs to the healthcare system have come down, reducing spend. In January 2012, healthcare spend was at 6.81% of the total annual plan (each month would represent about 8.33% if spread evenly) indicating that the reforms are keeping spending on track. These savings are reflected in market figures⁶⁶:

- Average retail prices of reimbursed medicines are down 5.7%
- Patient co-payment levels have risen from 34% to nearly 38%
- The overall market for prescription drugs has decreased by PLN 2.7bn (€630 million) or about 14%
- Wholesale margins have been reduced from 9.78% to 7% with decreases planned to continue to 5%

6.5.2.2. *Quotas from MAH*

With Poland having among the lowest prices in Europe, (see figure 2) manufacturers have put into place quota systems at wholesale and pharmacy level.

During discussions with the pharmaceutical chamber, we learned and saw the list of products that were in shortage at the time of the interviews. Their conviction was that the shortages were due to exports. However, on further discussion, we learned that the following was the typical process for the products in shortage:

1. The pharmacy placed the order on their usual wholesaler. They would be informed, for certain products, that either the pharmacy itself, or wholesaler, no longer had quota or product.

⁶⁶ Impact of the new Reimbursement Act on the Pharmaceutical Sector in Poland, 27 November 2012, IMS



2. As a matter of recourse, the pharmacy would contact that manufacturer directly (with the increased administration and time this costs).
3. With proof of a prescription, the pharmacy would often be delivered within 48 hours. There were, however, a number of anecdotal cases where the pharmacy was refused by the manufacturer on the basis that they had gone over a “reasonable” allocation for their area.

With product being delivered within 48 hours, it is our view that the product was in the market and that access to the product was restricted by the MAH ostensibly to reduce parallel exports.

It should be added that though pharmacies can order directly from a number of manufacturers, they are then often faced with minimum purchase requirements that are very expensive to finance. One pharmacy referred to minimum order quantities of 1’000 PLN (€234) from a top 10 manufacturer. In effect, a shortage caused by conditions of trade.

6.5.2.3. Parallel Exports:

With among the lowest prices in Europe, and all stakeholders being dramatically affected, parallel exports are a given. Despite the fact the pharmacies are prohibited from exporting products, pharmacies anecdotally sell on a cash basis to parallel exporters, compared to 14-30 days for the typical reimbursement period. Wholesalers are careful with their involvement in this business to avoid being impacted by quotas but are apparently involved though other companies and agencies.

Anecdotally, the level of parallel exports has not, however, increased over the past few years and have remained the largely stable, although the composition of products have changed. The following table shows the price differences between various products in Poland and the key export market of Germany.

Table 11: Key price differences between Poland and Germany⁶⁷

Top 10 exported products	Dosage	Polish ex-factory price (€)	German ex-factory price (€)	Difference (+ %)
Clexane	PF SC SG 10K/1ML 10 0.4ML	20	39	95%
Eligard	DRY PF RT SG 22.5MG 1	192	356	85%
Fragmin		18	48	167%
Seretide	LUNG UD PWD NRF 250Y/DOSE+50Y/DOSE 60	24	36	50%
Serevent	LUNG UD PWD NRF 50Y/DOSE 60	16	81	406%

⁶⁷ IMS Poland - April 11



Top 10 exported products	Dosage	Polish ex-factory price (€)	German ex-factory price (€)	Difference (+ %)
Symbicort	LUNG MD PWD 160Y/DOSE+4.5Y/DOSE 60	16	30	88%
Vesicare	FC TAB 5MG 30	25	40	60%
Zoladex	DRY PF RT SG 10.8MG 1	196	396	102%
Average				132%

With prices ranging from nearly double that of Poland (at 95%) to four times, the concern of manufacturers regarding exports is understandable and the business case for exports quite compelling. Quantitative data is however missing and tables showing price differentials such as these lead to emotionally- and intuitively led conclusions that do not reflect the causes of shortages in their entirety.

6.5.2.4. Lack of financial capacity of pharmacies & wholesalers

In part due to the new Reimbursement Act, margins of pharmacies have reduced to levels where a community pharmacy struggles to meet their financial obligations. According to IMS, gross margins for pharmacies have reduced from 22% to 18%, essentially wiping out profitability for many. With decreases in sales recorded by 77% of pharmacies are further impacted (during the period of 9/2012 & 9/2011).

The dire financial conditions of pharmacies is reflected in reports that up to 70% of patients need to come to the pharmacy 24 hours after bringing their prescription due to limited stock availability at pharmacy level for reasons primarily linked to the inability of pharmacies to finance holding stock of various products.

We received a number of anecdotal reports of pharmacies not stocking product due to their inability to finance the stock. Therefore they were technically in “shortage” when patients came with prescriptions.

With decreased margins and prices, wholesalers will also need to take measures to reduce inventories and associated working capital costs. This may lead to product shortages for any major deviations in demand.



6.5.2.5. Reduced market access / reduction of product lines available (from MAH)

Due to the lower prices prevalent in Poland as well as the new legislation that has come through, there is evidence to suggest that manufacturers have removed products from the market as well as slowing the introduction of innovative products. It should be noted that generic manufacturers were also significantly impacted by the pricing structures in the market as well as the new legislation.

The regulation has reduced the number of available reimbursed products on the market. The figure stands at 1'380 products (including multiple presentations).⁶⁸ As was shown in the price differences table 6, without the ability of manufacturers to adapt price, a case such as this will make a market less interesting than others where better prices and profitability can be achieved. Manufacturers will, in other words, focus on markets that are more interesting commercially.

From virtually any perspective such forced differences in prices are not sustainable for any industry (for the products affected).

6.5.2.6. General manufacturing shortages

During our interviews, we learned of a number of manufacturing shortages occurring in the market. The reasons for these ranged from API shortages & production capacity issues to lack of orders at pharmacy level to quality/reimbursement/authorization issues.

Most recent are shortages of two newly launched products for pulmonary indications by local manufacturers Celon Pharma and Polfarmex. Their claim is that wholesalers have not ordered their products leading to shortages.⁶⁹

There have been other anecdotal accounts of locally produced insulin not being available though branded variants were, as well as the opposite.

In 2012 there were shortages of oncology products produced by Sandoz, which affected not only Poland but other markets in Europe.⁷⁰

6.5.3. Regulations in place on shortages - Market notification process

MAHs are required by law to notify the GIF of any prospective shortages. There are, to our knowledge, no requirements for pharmacies and wholesalers to do so and the government only now seems to become more aware of shortages on the market. Their primary concern

⁶⁸ Impact of the new Reimbursement Act on the Pharmaceutical Sector in Poland, Warsaw, 27 November 2012, IMS

⁶⁹ Shortages of newly-reimbursed medicines in Poland, Central Europe Pharma News Issue No.6 (91) - Wednesday, 20 March 2013, Pg. 11

⁷⁰ Poland: Shortage of Oncology Drugs Persists, Sebastian Gensior, 25 April 2012, Europe-Healthcare-EU, <http://europe-health-care.eu/poland-shortage-of-oncology-drugs-persists/#panel1-7>



has been to impose savings and having been successful at this, their attention is now being drawn to general shortages in the market.

6.5.4. Current consequences of shortages

A number of the causes and consequences of shortages in Poland have been listed. Due to these, prescribing patterns have also changed. Doctors have reduced prescriptions of (expensive) innovative drugs by up to 20%, in part due to increased co-payment requirements by patients while increasing prescriptions for non-reimbursed products.

6.6. Spain⁷¹

Spain has also been quite significantly hit by the financial crisis.

6.6.1. Available lists of shortages

Tracking of shortages can be done via the following URL:

<http://www.aemps.gob.es/cima/fichasTecnicas.do?metodo=buscarDesabastecidos>

This list is updated periodically and includes when the expected shortage will/has begun and when it is expected to end. Additional information is also presented when available including possible alternatives.

6.6.2. Definition/understanding of shortages by stakeholders

As in the case of Greece and the worst hit southern economies, spending on reimbursed medicines in Spain has fallen by 18.4% since 2009. It has been estimated by the *El Economista* newspaper that reimbursement levels in 2013 will be equivalent to those in 2004.

Sales of pharmaceutical companies have declined by an equivalent 15% on average with the number of prescriptions dropping by 6.1% in 2012 alone. Tied to this the average expense per prescription fell approximately 20% during the same period.

It is generally felt that the pharmaceutical market in Spain will continue to contract until 2016 (IMS) or 2020 (PricewaterhouseCoopers).

6.6.3. Primary causes based on analysis by stakeholders & interviews

6.6.3.1. Austerity and budget cuts

With extreme measures being taken to control cost in Spain, delays in payment to pharmacies for reimbursement has had an effect up the supply chain to manufacturers and is adding considerable risk and pressure on the possibility of shortages.

⁷¹ Spain research by birgli



Due to budget shortfalls, there are real concerns that the National Health System is no longer sustainable in particular with increasing levels of debts and periodic defaults (or threats of default) in various regions.

In Spain attempts are also being made to separate shortages with irregular supply and potentially access issues. Based on our review, however, there are no clear and general shortages of medicines in Spain though there are cases of irregular supply due to financing problems in some regions at any given time.

To tackle the issue of arrears, the government has enabled ICO (Institutional Official Credits) to pay providers for debt in 2012 and 2013. This will not prevent the situation arrears occurring again in the future.

A case in point that is often referred to was restricted credit by Roche to hospitals for a number of oncology products. This situation appears to have been resolved in the meantime.

Interestingly, some pharmacies feel that due to the crisis and severe pressure on sales, shortages have actually reduced as manufacturers seek to optimize their structures to eliminate any lost sales caused by controllable (internal) shortages.

6.6.3.2. *Parallel distribution*

Parallel distribution is often referred to as a cause of shortages in Spain, despite our review pointing towards irregular supply and access related issues. Based on anecdotal discussions with various stakeholders, the general impression is that parallel distribution has declined in recent years. Contributing to this are changes in pricing in the market and products going off patent from which generics have increased their market share from the low teens to over 34% over the last 5 years or so.

6.6.3.3. *Survey Summary*

Based on the answers we received in Spain, we have been able to weight the anecdotal causes of shortages with some key economic indicators. The following table includes ten statements made by the persons who answered to the questionnaire through during interviews. The point of view of some interest groups has become common knowledge because they make it permanently public in TV interviews, newspapers and professional congresses.

According to the significance attributed to the various causes for shortages, they have been assigned a weighting ranging from 5 (very important) to 1 (not so important).



Table 12: Survey summary - Spain

Statements made by Stakeholders	PHARMA COMPANIES	WHOLESALEERS	PHARMACISTS	AUTHORITIES	MARKET ANALYSTS
Prices and Regulatory Environment	5	5	5	5	5
ICO credit implementation to solve the Pharmaceutical debts of the CCAA	4	5	5	4	2
Low Prices for pharmaceutical products improve legal parallel exports	4	3	2	4	1
Social Security debts to Pharmacies for reimbursed	3	5	5	5	3
> Generics Market Share	5	4	4	5	3
European Traceability as solution for Shortages risk	4	4	3	5	2
References pricing System Implemented	4	4	4	4	1
Quotes system implemented In Spain	3	3	2	3	1

6.6.4. Market notification process

Shortages or irregular supply should be reported to the Spanish Agency of Medicines and Health Products (AEMPS).

In order to achieve a high level of traceability, all MAHs, wholesalers, and pharmacies are obliged to inform the MOH and their respective regional authorities of the legal entity to whom medicines have been sold within the territory.

6.6.5. Regulations in place on shortages

Spain has a number of regulations in place that have an impact on shortages. These include but are not limited to the following Royal Decrees (RD):

6.6.5.1. RD. 4 / 2010

This decree enabled the implementation of a reference price system (RPS). The RP of each category of product is categorized by cost per treatment per day with the target of a gradual decrease in prices estimated at 30 % to 50 %. The process was accelerated, however, with prices to go immediately to the minimum price of the first generic in the market.

The effect of this decree saw a decrease in prices of product as well as the unit volume of sales.

6.6.5.2. RD. 8 / 2010

This decree saw an immediate price reduction of 7.5% to all the products financed by SNS (Health National System). Generics were exempted.



6.6.5.3. RD. 9 / 2011

This decree, among other items, provided for additional reduction of 7.5% for branded products which have been on the market for more than 10 years and do not have a generic version in Spain

6.6.5.4. RD. 16 / 2012

This decree introduces the implementation of a co-payment system implementation and new for the individuals covered under the Spanish National System of Health. It also institutionalised centralised purchasing for hospitals and centralised tendering for certain medicines in retail.

The aim of the co-payment system is to reduce excessive use of medication. this measure will increase the average contribution of a patient from 5.8% to 10.63%.

6.6.5.5. Pending legislation

In March 2013 the Spanish government announced its intention to save an additional €395 million by removing the minimum price of medicines.

There is a general concern that should certain prices drop too far, manufacturers will no longer be interested to continue to supply the market with certain products.

6.6.6. Public service obligations

Article 43 of the constitution, as stated in the official state bulletin (BOE 29.12.78), establishes the right of all citizens to the protection of health. It is, however, clear that for such a right to be effective, the public administration should adopt the necessary measures to ensure its implementation

The Central Government should thus effectively guarantee the supply chain to the patient (via the pharmacy). Citizens are to have unrestricted access to the pharmaceutical products they require.

6.6.6.1. Circular 2/2012

This circular seeks to ensure that all stakeholders involved in the export of a certain group of pharmaceutical products, need to inform the Spanish Medical Agency of their of their intentions.

7. Recommendations

Over the course of our study we have come across many recommendations and (partial) solutions to the problem of shortages of (reimbursed) medicines. The few that we will propose will echo many of these and can be considered a distillation as well as a reflection. Nevertheless, for additional view points, we can suggest reviewing



recommendations from the PGEU⁷², EMA⁷³, GIRP⁷⁴, APPG⁷⁵, and many others too numerous to list again. We would like to thank everyone we interviewed for their ideas and apologise if we cannot adequately quote/reference each one.

7.1. Common Ground - the patient

A key point of common ground should ultimately bring us back to the patient. Throughout the document we have covered Economic, Business, and Supply Chain issues causing shortages with certain apparent cause and effect patterns.

Ultimately it is the patient who is or risks being affected and this focus should not be lost in the process.

7.2. Common threads

7.2.1. There are definitely shortages of medicines throughout Europe

We state the obvious here but all parties acknowledge that there are shortages and in every market they appear to be getting worse. Patients are getting affected, every day everywhere. Shortages need to be acknowledged as a Europe-wide problem.

7.2.2. Lack of a common definition

A clear approach towards one or more definitions of shortages, which can strengthen associations with cause, quantity, and duration, would support efforts towards addressing the issue.

7.2.3. Lack of data and the need for transparency

Throughout the study we noted how difficult it was to get quantitative data from each stakeholder of the process. Stakeholders have an opportunity to act now before legislation is enacted that, however well intentioned, may in fact not provide the best solution the industry can achieve for the benefit of patients throughout Europe.

Each member of birgli who has contributed to this study knows the supply chain intimately. We know that each stakeholder has their own data regarding the movement of product through the elements of the supply chain they directly control.

⁷² Medicines' shortages in the EU (PGEU Fact Sheet), 4 June 2012, Ref: 12.04.06E 005FS

⁷³ Reflection paper on medicinal product supply shortages caused by manufacturing/Good Manufacturing Practice Compliance problems, European Medicines Agency, 22 November 2012, EMA/590745/2012, Patient Health Protection

⁷⁴ Medicines Shortages in Europe and their Impact on Patients - Reflection Paper, GIRP, December 2012

⁷⁵ APPG Pharmacy - Report of Inquiry Into NHS Medicines Shortages, 15 May 2012, <http://www.appg.org.uk/APPG%20Pharmacy%20-%20Report%20of%20Inquiry%20Into%20NHS%20Medicines%20Shortages.pdf>



The issue at hand is not a lack of data, but an unwillingness to share it by each stakeholder, and we do mean each stakeholder. Although the sharing of this data may be the political and commercial equivalent of Pandora's box, we feel that it will be difficult to engage in a meaningful dialogue on the subject without full disclosure.

In our view, full disclosure or near to it, is likely to be legislated in the mid-term unless the shortages issue dramatically improves.

With transparency on product flows, informed decisions can be made on what types of measures need to be taken and in what area of the supply chain.

7.2.4. Lack of communication

Though the EMA is in the process of consultations regarding shortages including timelines to review various areas, there appears to be little coordination between European Authorities and member states and less between regulatory bodies and the various stakeholders.

This ties in with the lack of data and transparency. Improved communication is a critical component for all stakeholders going forward.

7.3. Centralized & Member State recommendations

7.3.1. Centralized reporting - use of the "Rapid Alert System"

We have noted that shortages are occurring in all the markets we have reviewed. To date there is no centralized oversight to review patterns across countries. Manufacturing & supply chain related shortages potentially affect more than one market and may have certain commonalities in place.

Mechanisms exist today that can be used to alert member states of shortages in other markets. One of these is the "Rapid Alert System" which is today used for pharmacovigilance to track adverse reactions and other issues with pharmaceutical products.⁷⁶

We would add that this idea came from an interview with an official in one of the member states. There are good ideas and concepts in the markets.

7.3.2. Strengthen current central legislation to rapidly move products to areas of shortages

As described in Section 5 - Regulation there is already a strong legal framework in place surrounding the obligation of continuous supply and issues linked to manufacturing and cessation of marketing. The language of this legislation could be strengthened to include

⁷⁶ European Medicines Agency, Rapid Alert Procedure, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/wrapper_product_defects_alert_procedure.jsp&mid=WC0b01ac058006bf89



products in shortage and the ability of countries to source products from other markets, even if not in the registered packaging labelling or name, on an emergency basis. Such strengthening will need to include measures to remove/limit speculative pricing or other predatory practices.

7.3.3. Create a central unit of all stakeholders to review and develop solutions together with legislative bodies (central and national)

Currently great care is being taken by each of the stakeholders not to infringe the free movement of goods and other principles of free-trade within the European Community. We would like to repeat a statement made earlier in this document:

“In essence many basic concepts of a free market such as setting of prices are at best marginally present in the pharmaceutical industry”

Where specific price, production, availability and other controls are already in place, the concept of a fully free market becomes difficult to apply adequately. This is even more the case when the health of all citizens is at stake. A discussion between all stakeholders needs to take place without the fear of legal and political reprisal to find solutions to shortages.

Each of the stakeholders we have spoken to are prepared to enter into group discussion but each will need to be prepared to “give-up” certain elements of recourse typically available because the healthcare market operates differently to most others.

There will be the concern of precedent and the question “where does this stop?” from each stakeholder. We do not have answers for this important question.

7.3.4. Legal “Teeth”

Clear legal and financial consequences of shortages would also encourage an improvement of the situation. Application of consequences would provide the stakeholders involved a benchmark against which to determine where the consequences would be more costly than shortages. Where and how to apply consequences would be a complex challenge, however.

7.4. Practical Recommendations

A number of interesting and creative solutions were proposed by various stakeholders and are in place in various markets.

Beyond the centralized recommendations some critical proactive action can be taken now by various stakeholders:

7.4.1. Providers (hospitals, pharmacies)

Standard operating procedures for shortages can be implemented at member state and association level on how to manage shortages as they occur. This can include general guidelines on substitution (member states restricting this may need to re-evaluate their



policies) to guidelines on how to ration the use of certain products until the shortage situation has been resolved. There are numerous examples of such guidelines, some of which can be found in our bibliography.

7.4.2. Trading companies (wholesalers, parallel distributors)

As mentioned earlier, one parallel exporter has communicated with the pharmacies supplying them that, should there be shortages in their pharmacies, they would be prepared to return the product (at no mark-up). Though this may not always be practical, simple solutions such as these could reduce the impact of a given shortage.

To extend on this concept, multi-national wholesalers have the means to review product availability in affiliates in other countries for products in shortage and could facilitate the movement of product to markets where shortages are currently ongoing. This could be tied into the “rapid-alert” mechanism we referred to.

7.4.3. Systematic approaches

There are numerous systematic approaches to dealing with shortages and developing strong SOP's. These range from an “Incident Management Approach” to “CAPA” (corrective and preventive actions) which can be looked up and implemented.

8. Conclusions

There are many causes for the current shortages facing patients in the market today with no single primary cause from our perspective although admittedly there is limited quantitative data to support this assumption either way. There are already a number of potential solutions/improvements that can be implemented quite quickly which would help reduce the shortages the markets currently experience.

We need to be reminded that a patient centric focus should be emphasized and not only the commercial and legal/political aspects of the pharmaceutical industry.

The impact of austerity and the economic situation on patient outcomes also needs to be reviewed. What can actually be afforded by different member states is an important challenge for all stakeholders.

Solutions need to be driven centrally and coordinated locally as shortages are not isolated in each market and there are definite cause and effect patterns visible within and between member states.

We encourage dialogue to begin between all stakeholders to reduce, manage, and ideally prevent shortages of medicines from occurring and impacting patient outcomes.

Commercial stakeholders should consider finding solutions quickly, as failure to do so will result in legislated solutions.



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9.4.3. birgli analysis

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10. Glossary

Term/Abbreviation	Definition
AEMPS	Agencia Española del Medicamento y Productos Sanitarios (Spain)
ANSM	Agence nationale de sécurité du médicament et de produits de santé (The French National Agency for Medicines and Health Products Safety - formerly AFSAPPS)
API	Active Pharmaceutical Ingredient
CMU	Commercial Medicines Unit (UK)
DTP	Direct to pharmacy
EMA	European Medicines Agency



Term/Abbreviation	Definition
EOF	National Organization of Medicines (Greece)
FMD	Falsified Medicines Directive
JIT	Just-in-time
MAH	Marketing Authorization Holder
MCS	Manufacturer Cannot Supply
PSO	Public Service Obligation
RP	Reference Price
RPS	Reference Pricing System



11. Who is birgli® ?

- birgli® is a management consulting platform of senior and well experienced independent executives with a primary focus on the healthcare distribution market.
- Established January 2006, birgli® is present in Europe, South East Asia and has a strong network in the United States, CIS, and the Middle-East.
- birgli® provides consulting support in the areas of Mergers & Acquisitions, Finance, Management Support, Business Development, Healthcare Distribution, Purchasing, IT, and Healthcare Marketing & Sales.
- More information on birgli®, our areas of expertise, and our team can be found at www.birgli.com.