Study on the Availability of Medicinal Products for Human Use

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FINAL REPORT

Disclaimer

This study report is presented as a working document to the Pharmaceutical committee and should be read in conjunction with comments of that committee that are being published in parallel. In particular, attention is called to comments of members of the Pharmaceutical committee regarding some factual mistakes identified in the report.

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1.0 Executive Summary

This study investigates the availability of medicinal products for human use in the EU and EEA, focussing on the authorisation procedures for medicinal products, a principal area of EU competence[1]

For the purposes of this study, availability of medicinal products is understood to mean the availability to patients of medicinal products in a pharmacy setting. Following the Terms of Reference and due to the fact that the majority of existing information refers to availability of individual products, the study uses medicinal products for human use as the unit of analysis. However, in most cases it is the limited availability of active substances rather than limited availability of individual products that constitutes a public health risk. Therefore, where possible, the study also aims to explore the public health implications associated with non-availability of active substances.

In addition to collecting and analysing the data on availability, the study also investigates the problem drivers and examines the effectiveness of existing European legislative provisions in addressing these problems, making recommendations where relevant.

1.1 Study approach

The study consists of three work packages, which look at three interrelated areas concerned with the availability of medicinal products:

- WP1: Extent of the problem
- WP2: Problem drivers
- WP3: Impact of existing measures

The work packages are based on stakeholder consultation with National Competent Authorities (NCAs), industry stakeholders, and other relevant stakeholder organisations, as well as literature review and review of relevant quantitative data. Each of the work packages is reported on in a separate section of the report. In addition, six in-depth case studies exploring particular issues relating to the availability and authorisation of medicinal products have been developed. The case studies focus on:

- the use of the Article 126a of Directive 2001/83/EC (Cyprus Clause);
- the use of Article 81 of Directive 2001/83/EC to address supply disruptions and shortages;
- the use of the Common Baltic Package Procedure;

[1] . In terms of medicinal products for human use, the Directorate General for Health and Consumers (DG SANCO) has responsibility for guaranteeing the highest possible level of public health and to secure the availability of medicinal products to citizens across the European Union, based on the principle that the placing on the market of medicinal products is made subject to the granting of a marketing authorisation by the competent authorities.

- the availability of cancer products;
- the availability of paediatric products; and
- the availability of herbal and homeopathic medicinal products.

The case studies were selected to cover a wide range of availability issues linked to EU pharmaceutical legislation. Three of the cases look at authorisation and other availability issues relating to specific types of products and relevant provisions (i.e. HAMPs and herbal medicines; neonatal and paediatric medicines; and cancer medicines). Two case studies look at specific types of availability issues and the use of specific EU provisions to address them (i.e. authorisations and marketing in small markets and use of Cyprus clause, and shortages and supply disruptions and the role of Article. 81, public service obligations and GMP legislation). The remaining case study looks at a specific availability issue, a non-European measure to address it, and how it relates to European provisions (i.e. impact of packaging and labelling on availability and the CBP).

As with the three main work packages, the case studies are based upon stakeholder consultation, literature review, and quantitative data.

1.2 Study findings

Extent of the problem

The study identified three broad types of unavailability:

- products not being authorised;
- products being authorised and not marketed; and
- products being authorised and marketed but unavailable due to shortages and supply disruptions.

Analysis of existing quantitative data has shown that there are indeed differences in the number of products authorised across the EU. This number ranges from approx. 2,000 to over 5,000 in some Member States. Although non-authorisation of products is seen as problematic by some of the stakeholders consulted, the differences in number of products authorised do not necessarily reflect differences in the number of active substances available, that is, the active substance in question may be authorised under a different product name It is therefore not possible to fully determine the public health implications of these differences.

Differences in the number of authorised products across Member States may in the first instance be related to the fact that manufacturers can choose different routes to authorise their medicinal product. These procedures include:

- **Centralised procedure (CP)** administered by the European Medicines Agency (EMA) and valid in all EU Member States. The procedure is mandatory for some groups of products (i.e. HIV/AIDS products, cancer products, or designated orphan products)
- **Decentralised procedure (DCP)** allowing for a simultaneous authorisation of a product in a selection of EU Member States

- **Mutual recognition procedure (MRP)** allowing for an authorisation in one Member State to be recognised in other Member States
- **National procedure** allowing for authorisation of a product in a single Member State

In addition, European pharmaceutical legislation established simplified national registration procedures for selected homeopathic and traditional herbal medicinal products, allowing for registration of these products without the requirement to submit some of the documentation required in standard procedures.

Centralised procedure is the only procedure that ensures authorisation of a medicinal product in the entire EU. However, on average, CP-authorised products account for less than 20% of medicinal products authorised in a given Member State. This means that Member States need to rely on other procedures to bring products onto their markets, which may result in significant differences in the number of products authorised.

Stakeholder consultation suggests that non-authorisation drives availability problems in Cyprus, Estonia, Iceland, Latvia, Malta, Slovakia and Sweden. Inability to secure product authorisation can therefore be said to negatively impact on availability in some, but not all, smaller markets, as well as in selected larger Member States. Analysis by product use (using the Anatomical Therapeutic Chemical Classification System, or ATC codes) has shown that the differences in the number of products authorised translate into differences in the range of products being available in individual Member States. This in turn suggests that certain medical needs may not be met or fully met as a consequence of unavailability of medicinal products.

A further issue identified in the study is the fact that authorised products may not be marketed in selected Member States. This has been identified as a problem in Belgium, Cyprus, Estonia, Finland, Hungary, Iceland, Latvia, Lithuania, Malta, Norway, and Sweden. This issue is particularly visible in the case of cancer products, which are currently authorised centrally, but where the number of products actually available in individual Member States differs substantially, as noted in the case study on cancer products.

Finally, supply disruptions and shortages are a problem reported in many of the consulted Member States, including larger ones. Such issues were noted in Austria, Belgium, Estonia, Hungary, Ireland, Italy, Lithuania, Malta, Norway, Sweden, and the United Kingdom. Case studies on the usage of Article 81 and on cancer products demonstrate that shortages can affect important products, such as those without substitutes, and force medical professionals to change treatment programmes, which can potentially put patients at risk.

Overall, lack of authorisation is only one of the availability problems in the EU and is not strictly limited to smaller EU Member States. This means that availability problems are not limited to small markets and an effective response to availability problems would need to take into account more than just issues relating to authorisation and focus on the EU as a whole. Nevertheless, ensuring that products are authorised remains an important starting point for tackling availability problems. Relatively few products are authorised centrally, and whilst the procedure is likely to become a more prevalent form of authorisation over time, efforts should

still be made to support a broad range of authorisation procedures and to assess how the interaction between authorisation and availability can be most effectively addressed.

Problem drivers

The table below provides the summary of the types of availability problems and the main problem drivers identified during the study, linking them to the main EU provisions aiming to enhance availability.

Table 1: Summary of Problem Drivers

Unavailability problem	Type of product	Possible Driver	Main EU provisions
Products not authorised	All products	Economic considerations (lower expected prices, smaller market size)	Mechanisms to place products on the market justified public health reasons in the absence of authorisation (Article 126a of Directive 2001/83/EC)
	All products	Dossier upgrading, where some authorisations are withdrawn as authorisations are updated to conform with EU *acquis* following accession	Mechanisms to place products on the market justified public health reasons in the absence of authorisation (Article 126a of Directive 2001/83/EC)
	Paediatric products	Perceived costs and ethical issues associated with clinical trials involving children	Obligations and rewards in the Paediatric Regulation 1901/2006
	Herbal medicinal products and homeopathic and anthroposophic products (HAMPs)	Divergence in national procedures and approach to herbal medicinal products and HAMPs	Legal framework set out in Article 13 and Article 16 of Directive 2001/83/EC and in Directive 2004/24/EC on Traditional Herbal Medicinal Products
Products not marketed	All products	Economic considerations: Lower expected prices and smaller market size compared to costs (i.e. pricing and reimbursement costs, administrative costs, transport and wholesaling costs, packaging costs)	Obligation to supply medicinal products when on the market; linking supply to authorisation (Article 81 Directive 2001/83/EC) Transparency Directive (89/105/EEC) aims to make negotiation processes more transparent
	All products	Time delays resulting from pricing and	Transparency Directive (89/105/EEC) sets

Unavailability problem	Type of product	Possible Driver	Main EU provisions
		reimbursement procedure	deadlines for pricing and reimbursement decisions
	All products	Language labelling requirements, especially in smaller markets	Possibility for companies to produce multi-lingual packs for multiple (small) national markets (Article 63 of Directive EC/2001/83)
Supply disruptions and shortages	All products	Small number of manufacturing sites and a global supply chain are prone to disruptions.	Obligation to supply medicinal products when on the market; linking supply to authorisation (Article 81 Directive 2001/83/EC)
	All products	Shortages linked to quotas and parallel export	Obligation to supply medicinal products when on the market; linking supply to authorisation (Article 81 Directive 2001/83/EC)

The problem drivers are varied, but economic considerations appear to be the main factor behind products not being authorised or marketed in selected Member States. These economic considerations include low expected prices and small market size compared to costs of authorising and supplying a product

Purely regulatory problem drivers can mainly be linked to unavailability of specific product types. This includes for example herbal medicinal products and HAMPs, where simplified registration procedures are viewed as broadly appropriate but their incomplete and ineffective implementation in Member States seems to result in relatively few products becoming registered as medicinal products.

Impact of existing measures

Consulted stakeholders generally view existing European provisions that aim at enhancing availability positively. Article 126a of Directive 2001/83/EC (Cyprus Clause) has been used in Malta and Cyprus to bring unauthorised products onto the market and whilst not being seen to be ideal is considered an important method of ensuring patient access to essential medicinal products in these countries. It is however worth noting that other Member States facing availability problems find the provision difficult to interpret, especially with regard to assigning of responsibilities when using the procedure, and instead choose other solutions.

Consulted stakeholders have mentioned that to solve availability problems, it is often less risky, more targeted and quicker to use Article 5(1) to bring a product onto a Member State instead of having to wait for a company to start a procedure as per Article 126a, especially when there is a pressing public health concern affecting an individual or a small number of patients.

Stakeholders have referred to this provision as a “life saver article” and many have expressed a preference to keep the article unchanged. A suggestion was made to extend the scope of the provision to cover multiple and potential patients, avoiding the repetition of the procedure and avoiding the risk of leaving untreated patients while the procedure is renewed.

The system of obligations and rewards in Regulation 1901/2006 (Paediatric Regulation) is also considered to be an effective tool for ensuring availability of products.

According to stakeholders, there is still room for improvement in some areas. In particular, European provisions concerning shortages and supply disruptions could benefit from further development at national level. Currently Article 81 of Directive 2001/83/EC, which sets out an obligation to supply, is the main provision addressing shortages and supply disruptions. As the case study on Article 81 outlines, the transposition and implementation of the Article appears fragmented, making the obligation to supply difficult to implement in practice, especially given changing pharmaceutical supply chains.

The European provision viewed by stakeholders as most problematic is Article 24 of Directive 2001/83/EC (Sunset Clause), setting out that an authorisation is to be invalidated if a product has not been placed on the market within three years of authorisation. Although the provision aims to ensure that products are marketed, according to the consulted stakeholders the use of the provision may result in the invalidation of authorisations for products which, although they are not marketed at the time, the NCAs may want to help bring back on to the market in the future. Existing evidence appears to confirm this view, showing that even with potential exemptions in place, marketing authorisations do in fact become invalidated as a result of the Sunset Clause.

1.3 Recommendations

There is evidently a need to better understand the relationship between authorisation and availability as it impacts on public health. Whilst reduced availability may impact on public health, it is inextricably linked to the breadth of available active substances and consequent coverage for health need. Within this context there are two areas where the current European pharmaceutical *acquis* could be reviewed to enhance availability of medicinal products. One area concerns negative regulatory problem drivers and specific provisions where there may be room for improvement. The specific recommendations include:

- Revise or withdraw the Sunset Clause provision to avoid potentially reducing the number of authorisations in place in individual EU Member States
- Further clarify the responsibilities of individual stakeholders when using a Cyprus Clause procedure to make it a viable solution to availability problems for more Member States facing such problems
- Work to improve the national implementation of simplified procedures for herbal medicinal products and HAMPs
- Ensure a more effective transposition and implementation of Article 81.

However, the above provisions do not address the central problem driver, namely economic considerations which lead pharmaceutical producers to authorise and market their products on purely commercial grounds. The second area for review therefore concerns incentives for authorising and marketing medicinal products. One potential solution, put forward by some of the NCA stakeholders, could be to explore the possibility of using financial and non-financial sanctions and rewards to incentivise producers to authorise and market the products in more markets. In particular, the stakeholders pointed to the Paediatric Regulation, which awards patent extensions to producers authorising products for use in the paediatric population. It is however not clear to what extent such a system could be implemented for a much broader group of products. In addition, it would be important to ensure that products authorised and marketed correspond to the health needs of the EU population and that resulting rewards do not negatively affect market access for lower-priced generic products.

2.0 Introduction

This document is the draft final report for the **Study on the Availability of Medicinal Products for Human Use.** This report includes the study findings and draft conclusions and recommendations. Following this introduction, Section 3 of this report outlines key terms used in the study, while Sections 4, 5, and 6 contain the findings related to the three study work packages. Section 7 sets out the conclusion and the appendices contain detailed case study reports, as well as methodological notes, reference list, contact lists, an outline of the stakeholder consultation topic guide, and a legislation screening template.

2.1 Study Objectives

The study is informed by the European Commission's Health Strategy 2008-2013 and in particular the link between health inequities[2] and the availability of medicinal products. The Study Terms of Reference (ToR) are to assess the availability of medicinal products for human use within the EU and the EEA. The specific objectives are to:

- collect data on availability of medicinal products for human use across the EU and the EEA;
- analyse the data to identify unavailability problems, in particular in smaller Member States;
- identify the problem drivers; and
- analyse the impact of EU pharmaceutical legislation and its application on the extent of unavailability.

The study is carried out in collaboration with national competent authorities (NCAs) and the European Medicines Agency (EMA), and draws on consultations with European stakeholder organisations representing industry, patients, consumers, doctors, pharmacists, distributors and other interested parties[3].

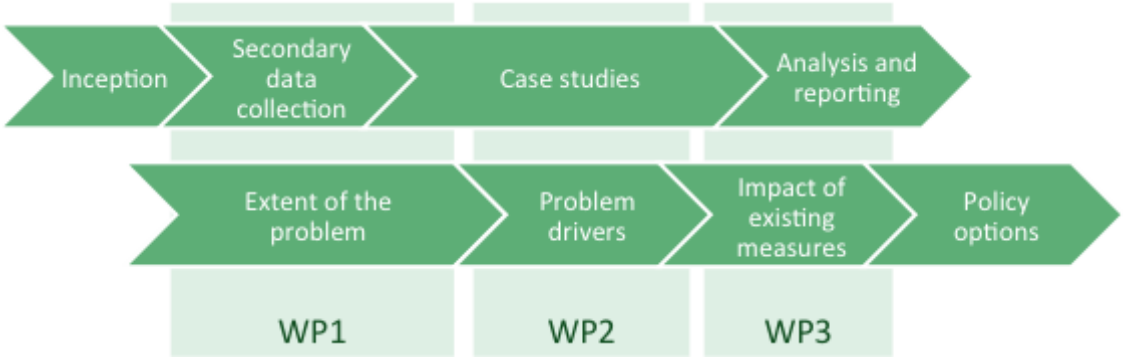
The study outputs are expected to inform policy options the European Commission could consider in order to address the issue of unavailability, notably in terms of better application of the current legislative framework. For this reason, the study aims to identify the regulatory problem drivers, with a focus on drivers that fall within the EU competences in the area (although a wider range of drivers will be identified) and in particular on EU legislation concerning marketing authorisation, which is a central area of EU competence. It is important to note that this legislation is centrally focussed on safety, quality and efficacy of medicinal products rather than availability. However, several provisions do help address unavailability issues and this means that an important element of the study has been to identify the provisions in the EU pharmaceutical *acquis* relevant to availability.

[2] European Commission (2007), ''White Paper - Together for Health: A Strategic Approach for the EU 2008-2013'
[3] See ToR

2.2 Study Structure

The figure below presents a broad outline of the study, showing the relationship between the study phases and the three main work packages.

Figure 2: Study design



The three work packages reflect the main objectives of the study. The work packages, their main objectives, and key tasks are outlined in the table below.

Table 1: Study work packages

Work package	Objectives	Main tasks
WP1: Extent of the problem	Compile data on the availability of medicinal products for human use across the EU and identification of the extent of the problem	• Stakeholder consultation • Interrogation of databases • Secondary data analysis
WP2: Problem drivers	Identify the causes of the problem	• Stakeholder consultation • Additional literature review
WP3: Impact of Existing Measures	Analyse the impact of measures already taken in the context of EU pharmaceutical Legislation on the extent of the problem/problem drivers	

3.0 Project scope

The study concerns on the availability of medicinal products for human use, with a particular focus on the authorisation of medicinal products. Authorisation procedures for medicinal products are an area of EU competence. Moreover, DG SANCO has responsibility for safeguarding the highest possible level of public health and to secure the availability of medicinal products to citizens across the European Union, based on the principle that the placing on the market of medicinal products is made subject to the granting of a marketing authorisation by the competent authorities.

For the purposes of this study, availability of medicinal products is understood as the availability to patients of medicinal products in a pharmacy setting. Although following the Terms of Reference the study uses individual medicinal products as the unit of analysis, it is the limited availability of active substances rather than limited availability of individual products that constitutes a public health risk. Therefore, where possible, the study also aims to explore the public health implications associated with non-availability of individual medicinal products.

Other key concepts of the study are defined as follows.

- a **medicinal product for human use** is defined by Directive 2001/83/EC as "any substance or combination of substances presented for treating or preventing disease in human beings" or "which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings"[4]

- **unavailability** refers to lack of access to medicines in a given market. it is important to distinguish between **temporary**, **constant** and **absolute** unavailability:[5]

    - **temporary unavailability** is usually unintentional, and mainly ensues from temporary manufacturing or wholesaling difficulties: with supply shortages, manufacturers may not prioritise smaller markets.
    - **constant unavailability** is usually intentional and results from a choice made by producers not to market a product in a specific Member State.
    - **absolute unavailability** represents a medicinal product simply not being developed in the first place due to low manufacturer interest. This is not of particular interest when analysing the problem of Member-State-specific unavailability.

- **a Marketing Authorisation (MA)** refers to the authorisation that needs to be obtained to market a product in a given market. This can be done through one of four procedures:

[4] Directive 2001/83/EC
[5] Heads of Medicines Agencies (2007), 'Availability of Human Medicinal Products – Report of Task Force of HMA MG', http://www.hma.eu/.../Availability_medicines_HMAMG_TF_Report.pdf

- via the **centralised procedure (CP)**, this is attained using a European Marketing Authorisation, which is valid throughout the EU (and the EEA).
- via a **national procedure (NP)**, marketing authorisation is exclusively sought for that Member State.
- via the **mutual recognition procedure (MRP)**, a product already authorised in another Member State is recognised in further member states.
- via the **decentralised procedure (DCP)**, where market authorisation is sought for a new product in one Member State via a national procedure and subsequently recognised by further Member States.

Additional concepts of importance to the study include the following:

- **Reference Member State (RMS)** refers to the EU Member State that conducts the primary review of the marketing authorisation application in the Mutual Recognition/Decentralised procedure and the Assessment Report of which is used as the basis for the mutual recognition of marketing authorisation[6]. A **Concerned Member State(s) (CMS)** is a Member State included in the mutual recognition phrase and expected to recognise the initial approval of the Reference Member State.

- **dossier upgrade** refers to the initiative to bring medicinal products' specifications/marketing authorisation in new EU Member States in line with EU legislation.

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[6] EMA (2010). Glossary (terms and abbreviations). http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/12/WC500099907.pdf

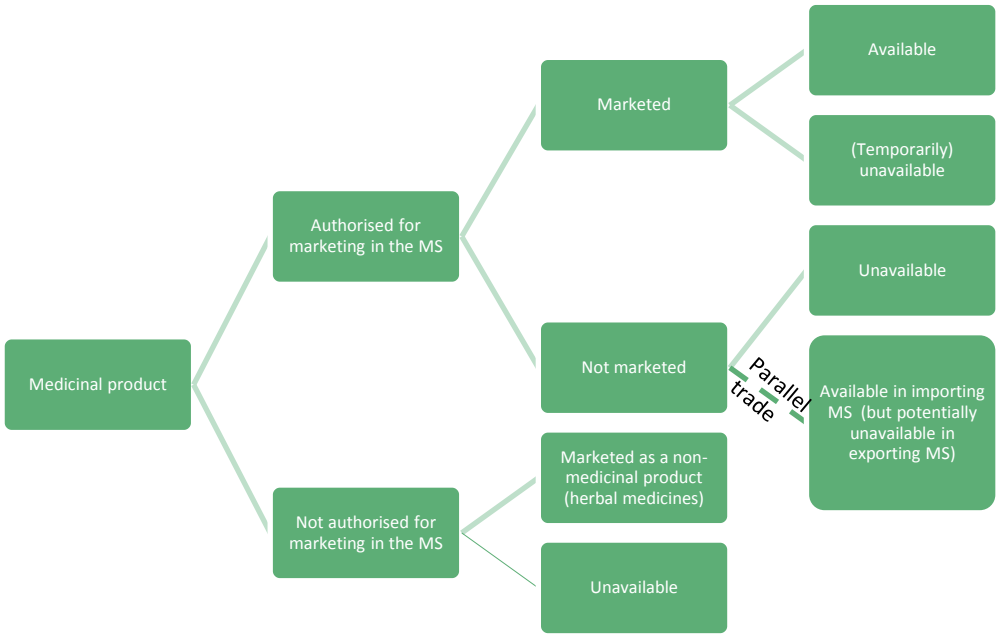
4.0 Extent of the Problem (WP1)

The first element of the study is to collect/collate available data in order to investigate the extent of the problem, namely the degree to which medicinal products for human use are available in individual Member States. The following section outlines the unavailability problems based on secondary sources and stakeholder consultation undertaken to date.

When examining unavailability, it is particularly important to take into account not only whether products are authorised and marketed, but also whether there are instances of them not being available to patients despite being authorised and placed on the market. Investigating this is of particular importance, since Article 81 of Directive 2001/83/EC (as amended by Directive 2004/27/EC) states that "[t]he 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 […]". This obligation to supply is discussed in more detail in the following sections and a case study (see Appendix I)..

The figure below outlines the various unavailability scenarios to be investigated.

Figure 3: Unavailability scenarios (outcomes)



The figure can be set against the three types of unavailability outlined in the previous section. Whereas lack of authorisation or non-marketing of a product can be seen as constant unavailability, a product that is marketed but still unavailable is more likely to be experiencing temporary unavailability resulting from, for instance, pricing and reimbursement issues or supply chain issues. This distinction is not necessarily clear-cut, since a very intermittent unavailability could lead to the product not being prescribed, resulting in a more constant lack of access. As mentioned above, it will therefore be important to investigate the practical application of Article 81 of Directive 2001/83/EC concerning the continuity of supply, as well as other relevant

Articles, such as Article 126a of Directive 2001/83 EC. In addition, it is also important to consider here the internal market and trade possibilities, which can subvert producers' segmentation of the market and make a product that is not marketed in certain Member States available to patients.

Finally, in order to arrive at an assessment of the current problem, findings concerning availability need to be seen within the broader context of health needs of patients in the EU and public health concerns in Member States. Although an in-depth assessment of health needs across the EU is outside the scope of the study, where possible, the following sections will aim to provide an indication whether availability problems are likely to result in unmet needs among the EU population or a public health risk in a specific Member State.

4.1 Number of Medicinal Products Authorised

As outlined above, the main focus of the study is the authorisation procedure and its impact on availability of medicinal products for human use. There are currently four main types of procedures available.

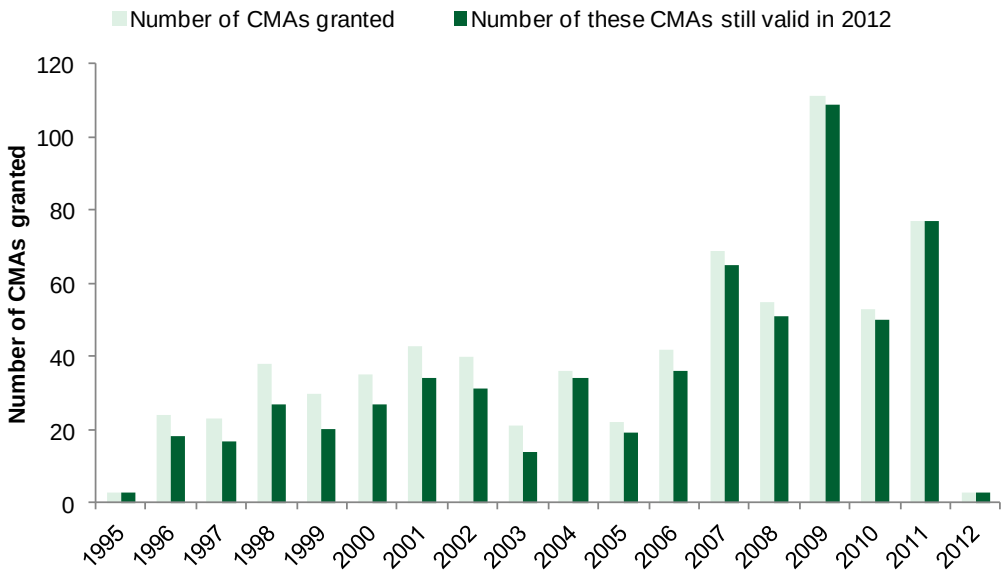
- **Centralised procedure (CP)** administered by the European Medicines Agency (EMA) and valid in all EU Member States. The procedure is mandatory for some groups of products (i.e. HIV/AIDS products, cancer products, or designated orphan products).
- **Decentralised procedure (DCP)** allowing for a simultaneous authorisation of a product in a selection of EU Member States
- **Mutual recognition procedure (MRP)** allowing for an authorisation in one Member State to be recognised in other Member States
- **National procedure** allowing for authorisation of a product in a single Member State

Despite the fact that the **Centralised Procedure** allows for the authorisation of a product across all 27 EU Member States, the number of authorised products differs substantially between countries. This is because manufacturer can choose among the other authorisation procedures, which remain widely used across the EU. The following sections outline the number of products authorised using these procedures to provide an overview of the total number of products authorised in different Member States.

Between 1995 and early 2012, 726 medicinal products for human use were approved via the Centralised Procedure. Of these, 90 were withdrawn or suspended at some point after being centrally authorised, i.e. there were 636 centrally authorised products in early 2012[7]. The figure below outlines how many central marketing authorisations (CMAs) were granted in each year since 1995, and how many of these authorised medicinal products remain authorised on the market in 2012.

[7] All data on CMA-authorised medicinal products was obtained from European Medicines Agency database, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125, accessed on 15 February 2012

Figure 4: Number of Central Marketing Authorisations granted (and still valid in 2012) between 1995 and 2012

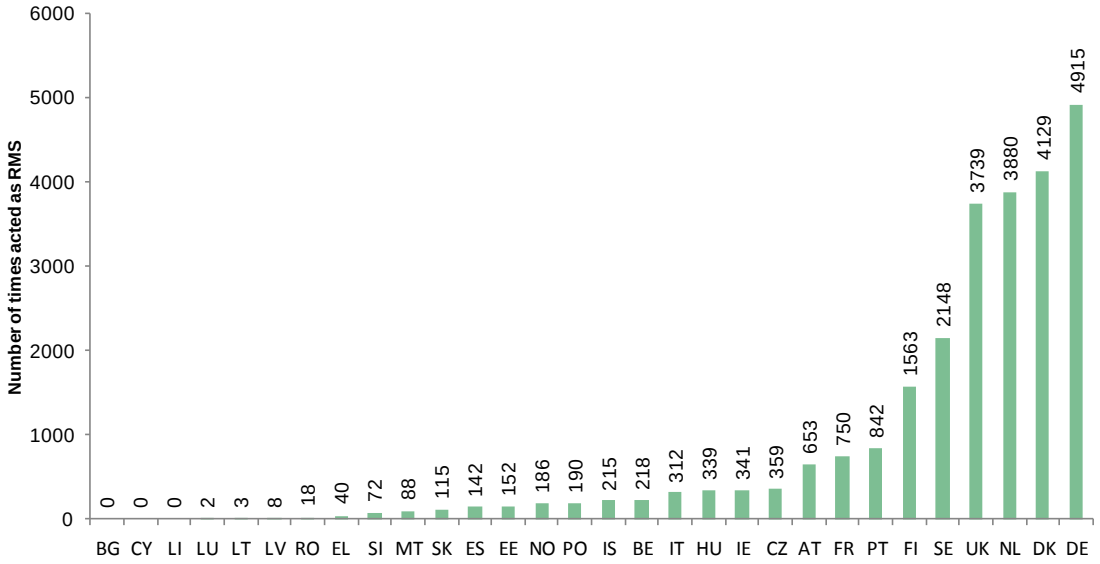


Source: EMA Database

In addition to the products authorised through CP, it is important to also consider the **Mutual Recognition Procedure.** According to the HMA Mutual Recognition Database[8], MRP has been used for 25,419 human medicinal products[9]. The figure below outlines how often specific Member States have been used as Reference Member State (RMS), up until early 2012.

[8] HMA Mutual Recognition and Product Index. Available at: http://mri.medagencies.org/Human/, accessed on 15 February 2012.
[9] Note that this includes medicinal products of the same name and active substance, but with different strengths, e.g. Vendal retard 10mg, Vendal retard 30mg, Vendal retard 60mg, etc.

Figure 5: **Number of times country has been used as a Reference Member State in a Mutual Recognition Procedure**



Source: HMA Database

The above figure does not necessarily reflect the differences in the number of medicinal products available in individual Member States. Although it is likely that the Member States used as RMS have more authorisations in place, it is also possible that a product is withdrawn from the Reference Member State once marketing authorisation has been granted, as has been the case in Finland[10]. The above figure also shows that in addition to Finland, some smaller Member States, such as Austria or Portugal, acted as RMS more or almost as often as some of the larger ones, such as France, Italy or Spain. Given that generally products are less likely to be marketed in smaller markets, as will be discussed in more detail in the next sections, this suggests that also these smaller countries may be chosen as RMS and not necessarily have all the authorised products marketed after obtaining authorisation.

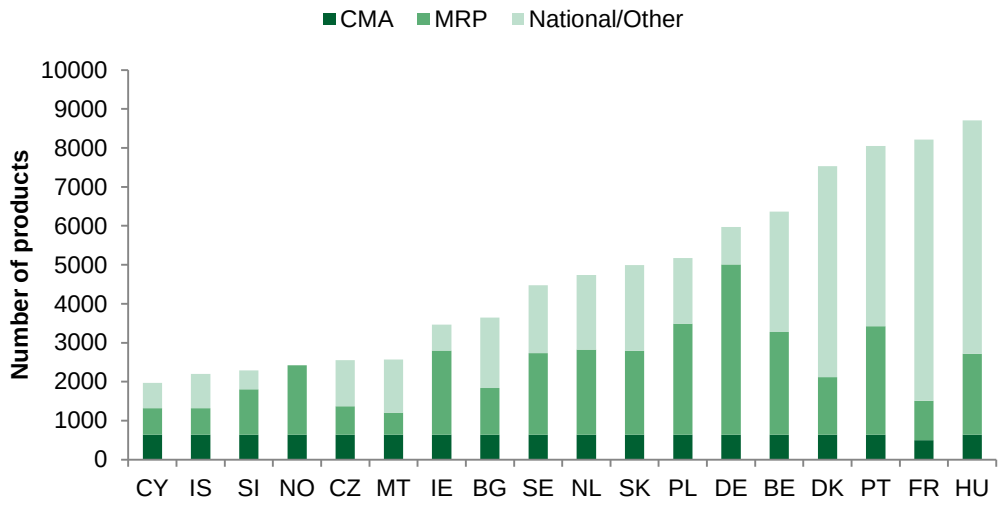
According to the HMA report[11], it is common that small countries are chosen as the RMS because of lower fees or more streamlined procedures. However, as suggested above, after mutual recognition by all the other **Concerned Member States** (CMS), the product would not necessarily be marketed in the RMS, potentially causing availability problems despite the product being authorised. At the same time, setting up lower fees for authorisation does not necessarily guarantee that the Member State is going to be chosen as a RMS more often. Stakeholders from smaller countries, such as Malta, have indicated that low fees in their Member States do not appear to have a significant impact on the authorisation of medicinal products.

In order to present a full picture of the number of medicinal products authorised for use in individual Member States it will be important to also consider **national procedures**, as well as

[10] Heads of Medicines Agencies (2007), 'Availability of Human Medicinal Products – Report of Task Force of HMA MG' and http://www.eahp.eu/content/download/25042/163194/file/NationalNews(5).pdf
[11] Heads of Medicines Agencies (2007), 'Availability of Human Medicinal Products – Report of Task Force of HMA MG', http://www.hma.eu/.../Availability_medicines_HMAMG_TF_Report.pdf

the Member States where the **Decentralised Procedure** is used to bring products to the market. The following figure outlines the total number of unique medicinal products (not counting package variations) authorised in selected Member States and broken down by route of authorisation.

Figure 6: Total number of unique authorised products



Source: EMA Database, HMA Database, National databases (BG, BE, CZ, CY, DE*, DK, FR, HU, IE, IS, MT, NL, NO, PL, PT, SE, SI, SK*)

Since the data above come from individual national databases of authorised medicines, there are comparability issues that need to be taken into account (described in more detail in Appendix II). Nevertheless, even taking into account differences in terms of defining what constitutes a unique product, the above figure shows that there are substantial differences between the number of products authorised across the EU. Although it is difficult to establish a direct correlation between size of the country (i.e. measured by population) and number of medicinal products authorised, some of the smallest EU and EEA Member States (Cyprus, Malta and Iceland) do appear to have some of the lowest numbers of products authorised.

A number stakeholders consulted during the study[12] noted that lack of authorisation is an availability problem. In particular, stakeholders in Latvia, Estonia, Cyprus, Iceland, Slovakia, and Malta have raised this issue, which is consistent with the above figure. However, stakeholders in Sweden also noted that Sweden sometimes faces problems due products not being authorised, showing that these problems are also relevant to larger Member States.

Another aspect related to non-authorisation is the withdrawal of authorisations. This has been noted by stakeholders in Malta and Cyprus in the context of dossier upgrading (discussed in more detail in the following section), but also in Netherlands where the interviewees noted that the authorisations for certain products tend to be withdrawn if the products are no longer

[12] See Appendix I for methodological notes and Appendix III for the list of consulted stakeholders

marketed[13]. This can potentially be problematic if there is a need to bring a product onto the market in the future.

The evidence presented above suggests that fewer products are authorised in some Member States than in others, and stakeholder consultation indicates that this contributes to the availability problems experienced in some Member States. However, in order to better understand the impact of these differences it is important to better understand whether and what needs are likely to be unmet when products are not authorised. This is discussed in more detail in the following two sections.

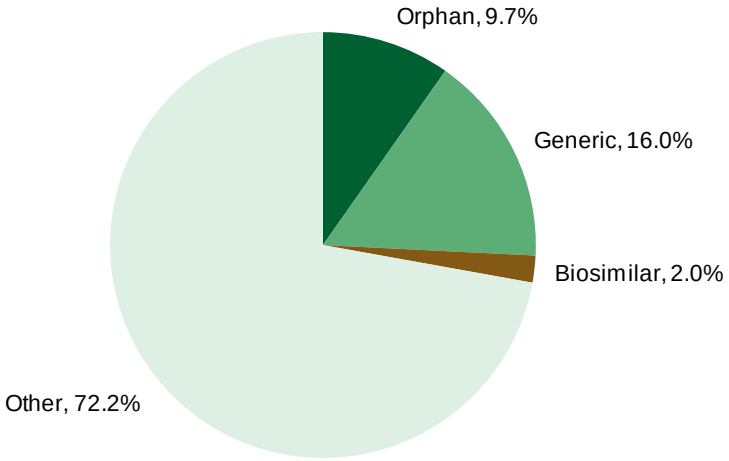
4.2 Number of Medicinal Products Authorised by Type

The above section outlined the overall differences in the number of authorised products in the EU. However, it is also important to explore availability of specific types of products, such as generic and originator or prescription and over-the-counter (OTC) products. The availability of the different product types is outlined in the sections below.

Generics and originator products

Looking at the centralised procedure, of the 636 CMA-authorised medicinal products on the market in 2012, 16% are generic medicinal products, 9.7% are orphan products and 2% are biosimilars[14], with the remaining products being originators.

Figure 7: Types of medicinal products with CMA in 2012



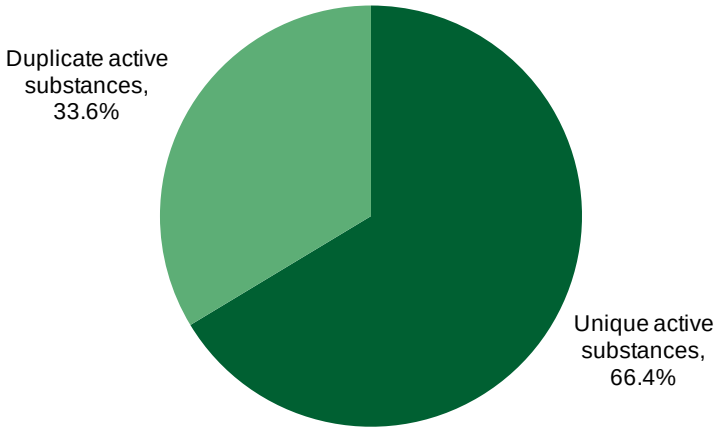
Source: EMA Database

Amongst the 636 CMA-authorised products on the market in 2012, there were 422 unique active substances used alone or in combination, whilst 214 products used duplicates of these

[13] The companies wishing to withdraw a registration in the Netherlands should state that an alternative is available and also make sure that their products are not available in the market, i.e. their stocks are completely sold out.
[14] Note that there is no overlap between these products

422 different active substances. This includes both generics, as well as potential multiple authorisations by a single applicant for the same product.

Figure 8: Different active substances within CMA-authorised medicinal products in 2012



Source: EMA Database

The two above figures do not provide information concerning availability of products in individual Member States as such, but they outline the profile of CP-authorised products. The figures suggest that products authorised in all EU markets are more likely to be innovative originator products, with lower-cost generic products using different authorisation routes. Therefore, looking strictly at authorisation, innovative products appear more likely to be authorised for marketing across the EU, including the smaller markets, than other products. This appears consistent with stakeholder consultation findings, where generic products have been identified as ones more likely to face availability problems by some of the Member States, in particular Finland, Latvia and Iceland.

It is important to note that the competition between generic and originator products and related intellectual-property issues can have an impact on the authorisation process and, as a result, on the availability of the product. One issue noted by industry stakeholder is the fact that the development of generic products during the patent period, currently allowed through the so-called Bolar provision (Art 10.6 of Directive 2001/83/EC) which sets out that studies and trials conducted during the patent period should not be considered contrary to patent protection, can be challenged in cases where third party suppliers are involved. This can potentially delay the introduction of generic products onto the market.

According to industry stakeholders, authorisation can also in some cases be linked to patent infraction proceedings (even if the two processes should be separate), once again resulting in delayed authorisation of some products. This is seen as a problem for instance in Portugal and, in the past, also in Italy. This statement is in line with the findings of the Pharmaceutical Sector

Inquiry Report[15], which indicated that originator companies may use a variety of instruments to extend the commercial life of their medicines. The report concludes that the behaviour of originator companies can contribute to a delay in the market entry of generic products.

By the strict definition of availability being 'availability as an authorised medicinal product in a pharmacy setting' and disregarding questions of affordability and access, limited or delayed availability non-availability of generic products could only be considered problematic from a public health perspective if an originator product is not available on the market. This is not likely to be the case in the situations described above.

Over-the-counter and prescription products

Looking at authorisations in individual Member States, it is possible to obtain some information about the proportion of OTC and prescription products among authorised medicinal products. For example, in Sweden, 92% of all authorised products are prescription products, while these proportions are 85% and 15% in Malta and 88% and 12% in Belgium. It is not possible to conclude from these data that there are substantial availability differences between these three Member States. Nevertheless, these figures are helpful in illustrating that across Member States there will be differences not only in terms of products that are authorised, but also in the way they can be accessed.

One issue noted with regard to the distinction between OTC and prescription products is the fact that, according to industry groups, applications to switch products to non-prescription status through a EU procedure are frequently rejected. According to industry stakeholders, given the fact that centrally authorised products (i.e. most recently authorised originators) need the switch to OTC status to take place centrally, producers set on supplying the product as an OTC product may withdraw it from the market if the switch is not accepted. In the longer-term, as industry stakeholders argue, this may mean that there would be fewer incentives for developing innovative self-care products Finally, the issue of switching the status of a product from prescription to OTC is also complex in the case of MRP/DCP procedure, where any changes in status in a given CMS would need cooperation with the RMS in question. As in the case of centralised authorisation, this could potentially lead to manufacturers withdrawing products from Member States where it is difficult to ensure the switch of status. Such issues are less likely to be the case for generic products that can use national procedures for switching.

A final availability problem that has been mentioned in relation to OTC products is the issue that, according to EU legislation, they need to meet more packaging requirements[16]. The increased costs associated with this may lead to the products being less commercially viable in some markets, which may in turn lead to the products not being authorised (or later marketed) in certain countries.

[15] See http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/

[16] Article 54(n) of Directive 2001/83/EC requires, in the case of non-prescription medicinal products, that the outer packaging or the immediate packaging of the medicinal product includes instructions for use in addition to the requirements that the packaging of prescription medicinal products need to meet.

It is worth noting that despite the potential issues identified by industry stakeholders, other stakeholder groups did not see issues concerning OTC products to be problematic from the availability point of view. A Finnish stakeholder also noted that OTC products are often less essential products and therefore availability problems regarding these products are likely to be less severe and should not raise public health concerns. Overall, the complexities relating to availability of OTC products do warrant further research. This is however beyond the scope of this study, which focused primarily availability to patients of medicinal products in a pharmacy setting.

Herbal products

Issues regarding authorisation have also been raised with regard to herbal products. Herbal products are defined by Directive 2004/24/EC on Traditional Herbal Medicinal Products (THMPD) as products "exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations"[17]. The Directive defines traditional herbal medicinal products as products fulfilling the following criteria:

- they have indications exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment;
- they are exclusively for administration in accordance with a specified strength and posology;
- they are an oral, external and/or inhalation preparation;
- the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience[18].

Under the revised Directive 2001/83/EC, a simplified authorisation registration procedure is established for these products.

Although the NCAs have not noted such products to be problematic with regard to availability, consulted industry stakeholders pointed out that the process of authorising products can take a long time (up to five years) and the approach to authorising such products can differ substantially between Member States. This makes it difficult for producers to bring such products to the market as medicinal products, potentially resulting in unavailability. Since the coming to force of Directive 2004/24/EC on Traditional Herbal Medicinal Products (THMPD), 572 products have been registered, with significant discrepancies across Member States (only seven Member States saw more than 20 products registered, and over 150 of all registrations were in Poland).[19] It is however not clear how these figures relate to products on the market prior to that time or to the demand for such products. It is important to note that some products

[17] Article 1 of Directive 2004/24/EC on Traditional Herbal Medicinal Products
[18] Article 1 of Directive 2004/24/EC on Traditional Herbal Medicinal Products
[19] AESGP (2012)

might already be available on the market as food substitutes, with any delay in authorisation procedures only relating to the products becoming available as medicinal products in a pharmacy setting. The availability of herbal medicinal products is explored in more detail in a case study in Appendix I.

Homeopathic and anthroposophic products

Homeopathic and anthroposophic products (HAMPs) are another type of product where there are potential availability problems. Homeopathic products consist of diluted doses of substances which in larger quantities would create the symptoms in a healthy person, while anthroposophic medicines are products that use natural substances and require "heat, rhythmic preparation and potentising methods"[20].

According to industry stakeholders, such products tend not to be registered, or the registration process is incomplete or outstanding. A study commissioned by the European Coalition on Homeopathic and Anthroposophic Medicinal Products (ECHAMP) found gaps in direct availability of HAMPs in five Member States investigated (Bulgaria, France, Germany, Romania and Spain) and identified availability issues even if a product were to be ordered. Like in the case of herbal products[21], unauthorised HAMPs, which have been introduced prior to the Council Directive 92/73/EEC could still be on the market under transition rules. According to an industry representative, certain products are available in selected Member States, but have no clear status. This also means that there are substantial variations in how individual Member States approach such products. These products are explored in a case study in Appendix I along with herbal products.

4.3 Health Impact of the Divergence in the Number of Authorised Products

Previous sections have shown that lack of authorisation is seen as an availability problem and there appear to be substantial differences in the number of products authorised across Europe. However, it is also important to understand to what extent these differences may impact on the health of the EU population. One way of doing so is to investigate whether differences in the number of authorised products mean that certain medical needs are not met. This can be done by looking at availability of products for particular conditions, as well as number of products authorised broken down by ATC (Anatomical, Therapeutic, Chemical) codes. ATC codes are a classification system for drug substances maintained by the WHO Division of Drug Management and Policies (DMP)[22]. They are used across a number of databases maintained by NCAs in individual Member States and therefore allow for comparing the availability of products for particular uses across Member States and make it possible to identify potential unmet health needs, especially where cross-country analysis of the availability of individual active substances is not possible.

[20] See http://www.echamp.eu
[21] PwC 2012
[22] The ATC code is a 5-level classification system, comprising:

- Level 1: products are classified by anatomical organ or system in fourteen main groups;
- Level 2 and Level 3: therapeutic/pharmacological subgroup;
- Level 4: therapeutic/pharmacological/chemical subgroup;
- Level 5: the individual substance.

The following table is an illustration of the differences in availability across Member States. It presents the number of authorised medicinal products for a selection of chronic conditions recorded in the 36th edition of Martindale's Drug Reference (2009)[23]. The table below serves as a representation of the differences across Member States. The approach taken was to map the authorised products to particular conditions (in this case selected chronic conditions) and to show the differences in availability across the conditions.

Figure 9: Number of medicinal products authorised for use in 17 Member States for a selection of chronic conditions

MS	Osteo/rheumatoid arthritis	Depression	Diabetes	Epilepsy	Asthma	COPD	Hypertension	Ischaemic heart disease	Total
DE	41	32	55	20	26	31	76	96	**276**
IT	54	23	42	19	28	36	67	89	**265**
PT	55	29	46	17	25	30	62	77	**256**
CZ	38	29	52	21	26	30	60	79	**251**
ES	51	27	37	18	24	30	64	82	**247**
FR	43	28	42	19	21	29	67	85	**247**
UK	42	27	48	19	23	26	65	79	**243**
AT	42	28	33	18	27	32	66	85	**239**
EL	40	20	44	19	22	27	61	76	**227**
BE	37	27	36	18	20	25	59	74	**219**
NL	36	21	49	18	19	22	59	71	**219**
HU	35	22	33	19	24	29	55	70	**210**
IE	36	24	36	17	21	24	54	68	**207**
DK	37	23	33	16	18	22	50	63	**195**
PL	27	22	47	16	19	22	47	58	**194**
SE	32	21	33	16	20	23	42	57	**183**
FI	31	21	31	16	20	23	46	58	**182**
								TOTAL	**549**

Source: Martindale (2009)

Although the above table focuses only on a selection of Member States and a selection of conditions (eight chronic conditions), there are considerable differences in the number of

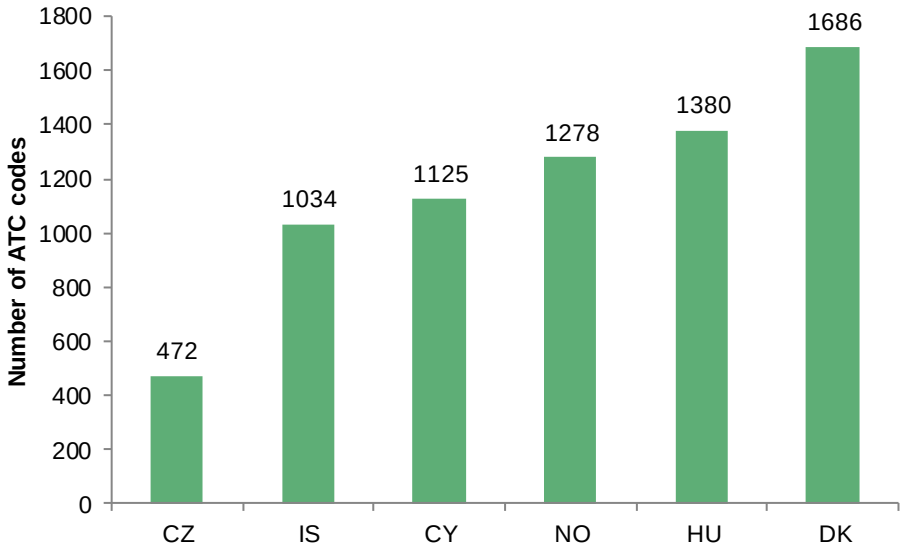
[23] See https://www.medicinescomplete.com/mc/martindale/current/login.htm?uri=http%3A%2F%2Fwww.medicinescomplete.com%2Fmc%2Fmartindale%2Fcurrent%2F. It is important to note that the database excludes those medicinal products that are administered only in a hospital setting. As a result, it is possible that, in addition to products outlined in the table, other products can also be available to patients in hospitals.

[24] Duplicates removed

products authorised in different Member States (for instance there are 276 products authorised for these 8 chronic conditions in Germany, while in Finland there are 182 products authorised for the same conditions). Therefore, one would expect that some of the patterns would be present if the analysis was to be conducted for the entire range of conditions. It is also worth noting, that, although some of the larger Member States are placed towards the top of the table (Germany, Italy, France, Spain and the UK), the relationship is not straightforward. For instance Poland, one of the larger markets in the EU, is one of the three Member States with fewest products authorised for these specific conditions. This is also the case when examining the number of authorised products for individual conditions. Although for most conditions Germany has the largest number of authorised products, in some cases smaller Member States have similar or larger number of authorisations.

The above analysis however looks at number of products rather than active substances, which means that it is not possible to conclude that some public health needs are not met. Another way of looking at availability by condition, which does make it possible to identify potential unmet needs, is to look at availability of authorised medicines by ATC code. The following figure outlines the number of unique ATC codes present in the authorisation databases in selected Member States. This provides an indication as to ATC code coverage, although it is important to note that there are differences between Member States, or even across a single database, in terms of the way ATC codes are assigned to individual products. This means, for instance, that where higher-level ATC codes are used, the figure below would underestimate the availability.

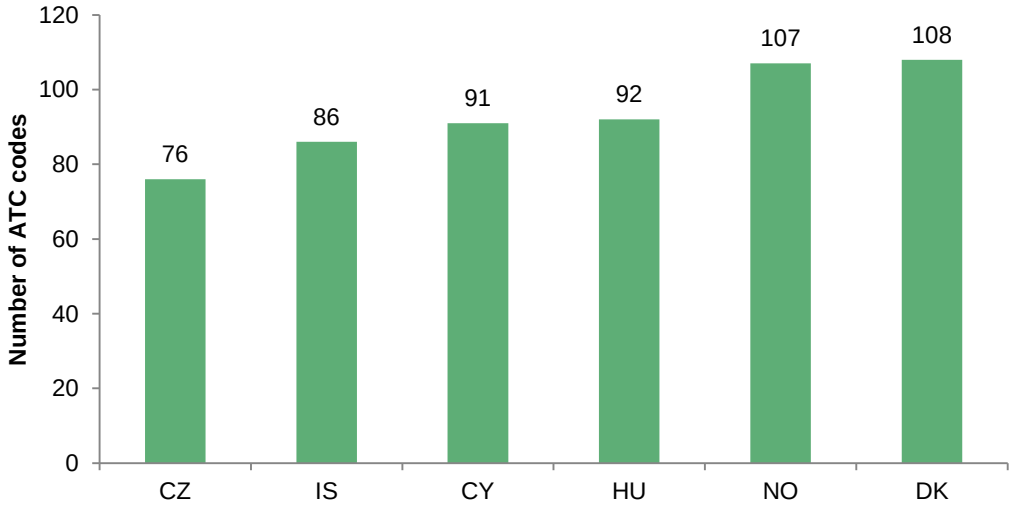
Figure 10: Unique ATC codes present in MS databases



Source: National databases (CZ, IS, CY, NO, HU, DK)

In order to ensure consistency, the following figure outlines the ATC code coverage by looking at the second-level ATC codes (i.e. C03).

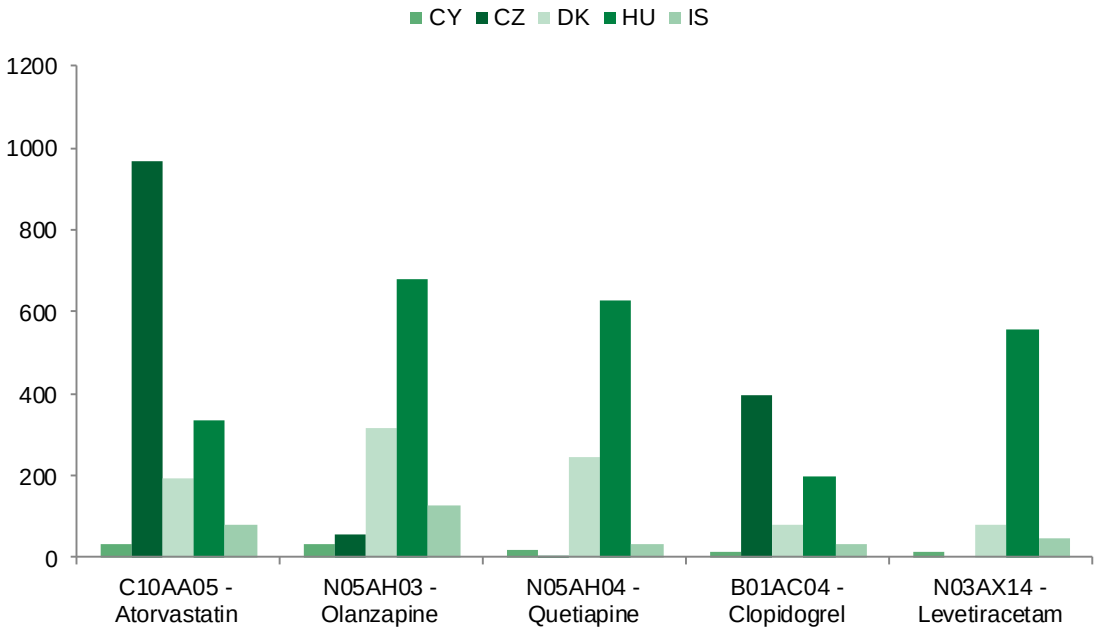
Figure 11: ATC code coverage by level 2 ATC code



The above figures show the differences in terms of coverage of ATC codes by medicinal products authorised in individual Member States, meaning that in Member States where a certain number of codes is not covered by authorised products, for some active substances and indications there would be no products available. Although the analysis by level 2 codes shows that the differences in coverage are relatively small, they are still in place and show that whole groups of products authorised in some Member States are not authorised in others. This suggests that it is possible that the needs of certain patient groups can potentially remain unmet using the available products. However, it is difficult to make a definite assessment without a comprehensive understanding of health needs across the EU, which is beyond the scope of this study.

Looking at more specific product groups, the figure bellow outlines the most common ATC codes for products in the selected countries, showing that even for the most common active substances and indications the number of authorised products differs substantially, with the number of products being much lower in smaller Member States such as Cyprus.

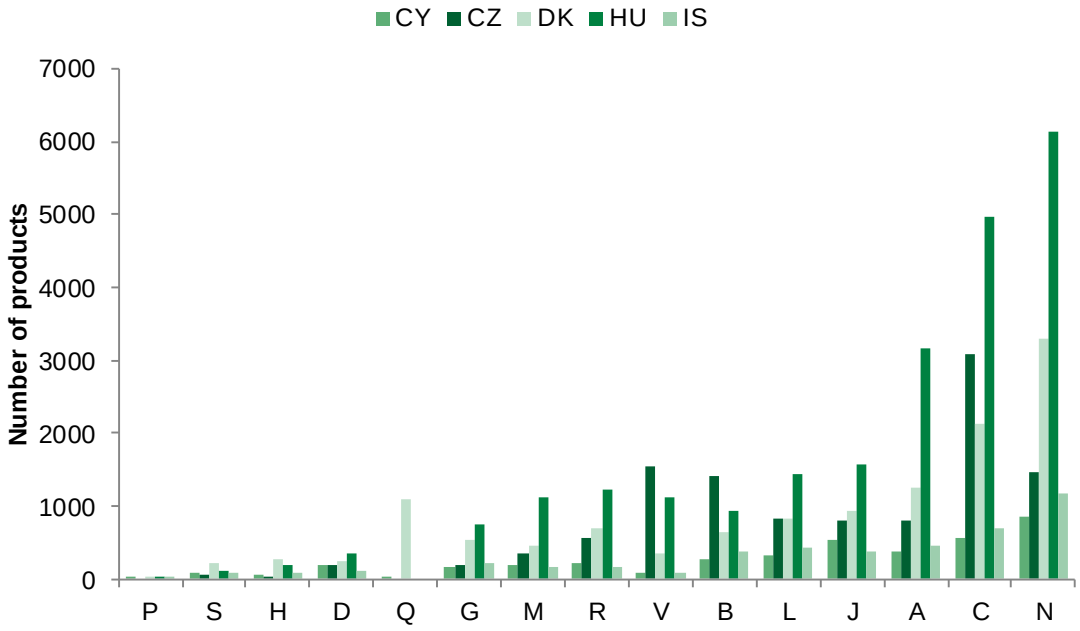
Figure 12: Number of authorised products by level 5 ATC code



Source: National databases (CZ, IS, CY, HU, DK)

The figure below shows the number of authorised products by first level ATC code, once again illustrating the differences in the numbers of unauthorised products between Member States.

Figure 13: Number of authorised products by level 1 ATC code



Source: National databases (CZ, IS, CY, HU, DK)

Consultation with stakeholders has pointed to some particularly problematic areas. Stakeholders in Cyprus noted that the products most likely to be missing from the market are products with ATC codes N (Nervous system), A (Alimentary tract and metabolism) and V (Various). Maltese stakeholders also pointed to lack of availability of certain types of products, such as those related to parasitic diseases (although these are also rare in Malta).

More generally, according to many of the consulted NCAs, products aimed at small patient groups are facing most availability problems (also in larger Member States – for example paediatric medicines facing availability problems in the UK), although the Lithuanian stakeholders pointed out specifically that availability is not correlated with rarity of the condition. In addition, consulted NCAs encountered issues related to anticancer medicinal products[25] (i.e. Austria, Cyprus, Hungary, Ireland, Lithuania and the Netherlands). It is however important to note that this also relates to products which are authorised but not marketed, discussed in more detail in the next section. The availability of paediatric products and cancer products are examined in more detail in case studies in Appendix I.

Lack of authorised medicines may cause problems for patients, physicians, consumers and governments, therefore unavailability of medicinal products is a public health concern across the EU[26]. Patients' health may suffer especially in case of conditions that require timely access to needed medicines and therefore healthcare outcomes might be negatively affected by unavailability of products for certain conditions, as the above analysis suggests[27]. According to the 2007 HMA Report, unavailability of medicinal products can affect public heath in the following ways:

- Unavailability may cause public health concerns if patients are untreated or treated with an unauthorised or an unsuitable product or a product for which information is limited or incomplete (e.g. licensed import of unauthorised products, 'off-label' use of products).
- Unavailability may cause public health concerns arising from untreated or ineffectively treated infectious diseases.
- Unavailability may cause public health concerns where patients obtain the medicine directly over the Internet, as medicines may not be appropriate or may be counterfeited.
- Unavailability may cause public health concerns about unclear procedures for pharmacovigilance of unauthorised products used by a physician for an individual patient.

In addition, unavailability may cause increased costs for governments and hospitals that need to carry out procedures to get hold of unauthorised products for individual patients and when unauthorised products used by physicians for individual patients are not reimbursed under usual conditions.

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[25] Anticancer products do not have a dedicated ATC code, making analysis by ATC code more complex.
[26] Heads of Medicines Agencies (2007), 'Availability of Human Medicinal Products – Report of Task Force of HMA MG', http://www.hma.eu/.../Availability_medicines_HMAMG_TF_Report.pdf
[27] Kanavos, P. et al (2011) The Pharmaceutical Distribution Chain in the European Union: Structure and Impact on Pharmaceutical Prices. Available at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/structimpact_pharmaprices_032011_en.pdf

4.4 Availability of Authorised Products

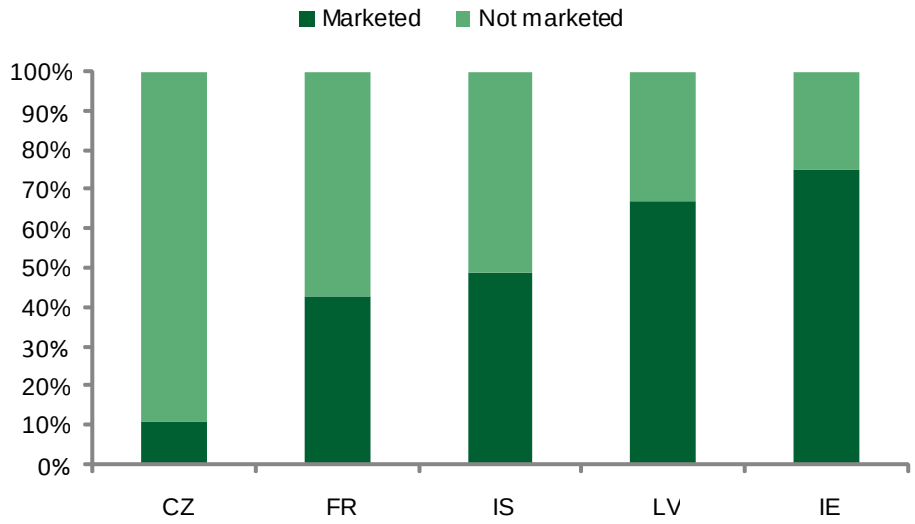
Previous sections outlined the differences in the numbers of authorised products across the EU and showed that these could impact on public health. However, in addition to availability problems occurring at authorisation stage, there are also availability problems occurring after a product has been authorised. Although these problems are not a principal focus of the study, unavailability of authorised products has been highlighted by a number of stakeholders consulted as being a concern in several Member States and therefore it is important for it to be addressed as part of this study.

Following the theoretical outline of unavailability scenarios (please see Figure 3 in Section 4.0 above), these can be broadly divided into two types of problems:

- products not being marketed (includes also products being withdrawn from the market); and
- products being marketed, but facing (temporary) supply issues.

The problem of **authorised products not being marketed**, regardless of the authorisation procedure, has been noted in a number of countries, in particular Belgium, Cyprus, Estonia, Finland, Hungary, Iceland, Latvia, Lithuania, Malta, Norway, and Sweden. One issue raised by some of the consulted stakeholders is the fact that centrally authorised products are often not marketed in all Member States, with a Latvian interviewee noting that only 10% of CMA-authorised products are marketed in Latvia. The figure below outlines the proportion of marketed and non-marketed products in selected Member States, based on national databases and stakeholder interviews.

Figure 14: Proportion of products marketed (all authorisation procedures)



Source: National databases (CZ, FR, IS), stakeholder interviews (LV, IE)

As can be seen in the figure above, the Member States with the largest proportion of non-marketed products are not necessarily the smallest Member States. Although market size has been noted by a number of interviewees as a key reason for products not being marketed, there are likely to be other drivers not directly related to size of the market, such as number of languages required on labels (i.e. in Belgium). These are discussed in more detail in the next section.

One aspect of the problems related to products not being marketed, identified by a subset of consulted NCAs, is the possibility of a product being withdrawn from the market. Stakeholders in Iceland noted that problems might occur when a patent for the product is purchased by another company, which in some cases chooses to remove the product from the Icelandic market. Stakeholders in Lithuania pointed out that a product may be withdrawn if the company chooses to market a more expensive replacement product, potentially resulting in affordability issues, or when a generic enters the market, resulting in the originator product being withdrawn, causing potential availability issues.

The second aspect of unavailability of authorised products relates to **shortages and other supply problems**. This applies to products that are generally marketed in the country. Such issues were mentioned by stakeholders in Austria, Belgium, Estonia, Hungary, Ireland, Italy, Lithuania, Malta, Norway, Sweden, and the United Kingdom. The nature of these supply issues varies:

- problems related to **manufacturing** were mentioned in Belgium and Ireland. These include issues related to manufacturing sites being temporarily shut down for various reasons and time needed to restart production. In particular, rising quality standards can mean that it becomes more difficult for producers to quickly restart aborted production lines. Products which are particularly affected include more expensive products

manufactured in smaller quantities or products which cannot easily be stored (i.e. insulin products);

- supply problems can also be due to **medical need**. In Norway shortages of antibiotics in 2011 and 2012 were linked to an unexpected increase in the cases of mycoplasma pneumonia; and
- certain products include active ingredients that require complex **logistical arrangements** or which are imported. These products can also be prone to unavailability. Hungarian stakeholders noted that this can be an issue with oncological products and vaccines.

Supply problems are particularly serious if there is no alternative to a given product. A Lithuanian stakeholder noted that this is the case with heparin, some anticancer medicines, such as fluorouracil, tamoxifen and some antibiotics (e.g. oxacillin, ampicillin with sulbactam).

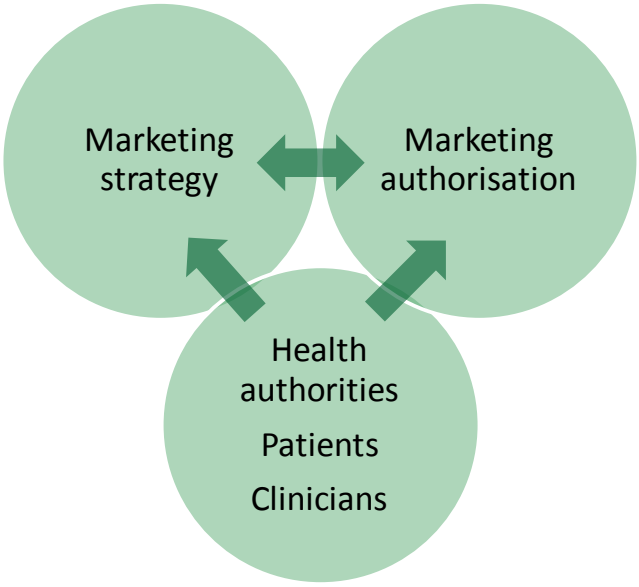
One final availability issue noted by wholesalers and also some of the NCAs (e.g. in the UK) relates to quotas imposed on wholesalers by the producers. If the quotas are exhausted, the wholesalers will not be supplied with further stocks of the product. The level of quotas differs between producers and Member States and in some cases may not be communicated to the wholesaler, affecting the wholesaler's ability to plan the supply of the product in advance. These issues are explored in more detail in the next section and in a case study focusing on shortages presented in Appendix I.

5.0 Identifying Problem Drivers (WP2)

The second part of the study focuses on problem drivers. The section above showed the different availability scenarios as a single chain that tracks the process of bringing a product on the market. However, in reality the interactions between different stages of this process (i.e. authorisation and marketing) can be complex. Business decisions to market medicinal products are likely to be taken prior to authorisation and industry stakeholders' approach to marketing authorisation in individual markets may be dependent on these decisions. This relationship is in part investigated in the following sections.

At the same time, as shown in the figure below, health authorities, as well as patients' and medical professionals' associations with an interest in securing availability, will aim to ensure that outcomes of both elements of the process lead to products being available.

Figure 15: Relationship between key stakeholders



This interaction is underpinned by a range of potential problem drivers behind unavailability of medicinal products. These can be broadly classified as:

- **corporate strategy**, including financial/business drivers relating to producers' perceived costs, benefits, resulting profit margins or returns on investment in particular markets, as well as business drivers relating to the broader supply chain;
- **regulatory system** drivers, relating in particular to authorisation of medicinal products. There are other important drivers such as pricing and reimbursement, but they are largely outside of the European Commission's competence and, although they will need to be taken into account, they will not constitute a focus of the study[28];
- **national health systems** and medical heritage; and
- **other external drivers,** such as unexpected supply chain disruptions[29].

The study explores mainly the regulatory **drivers** relating to authorisation, but it is not possible to view these drivers in isolation. Therefore the analysis goes beyond regulatory drivers and

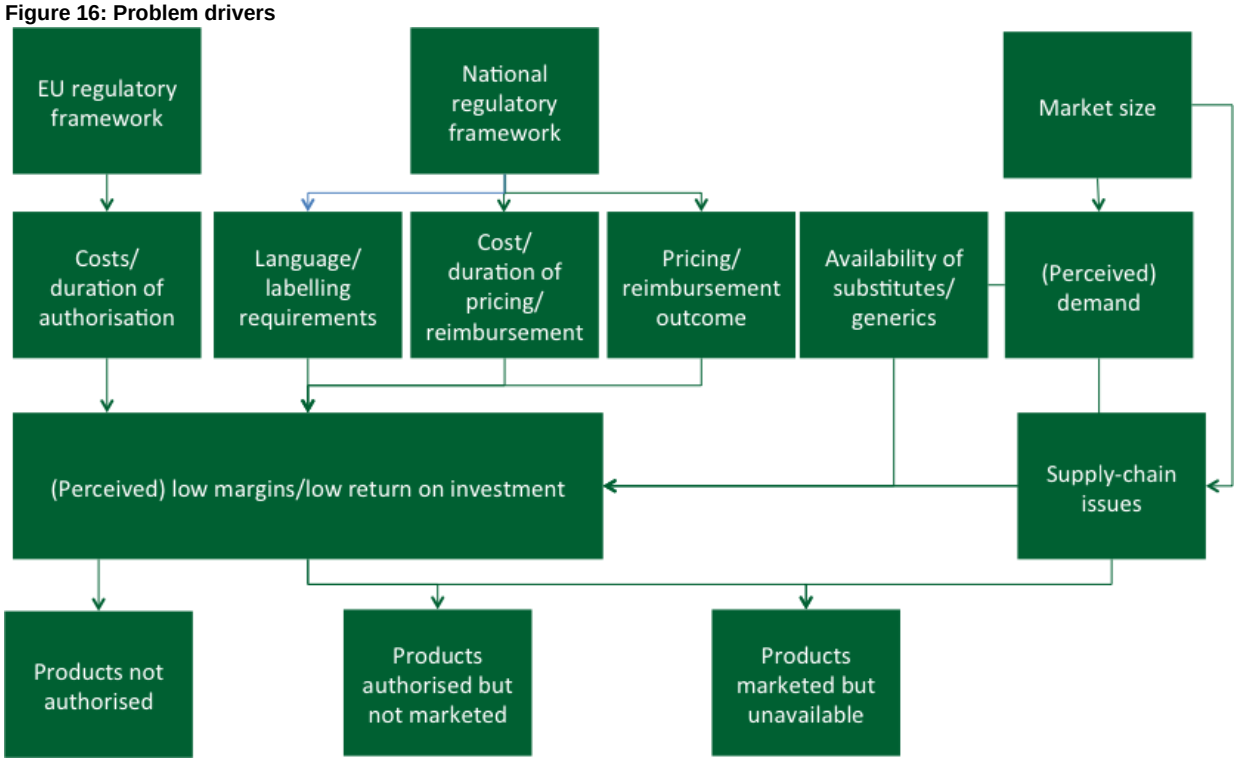
[28] Despite the limited competences of the European Commission in this area the Commission has presented on the 1st March, 2012 a legislative proposal which is the revision of the Transparency Directive. The legislative proposal aims at enhancing the transparency of national procedural rules concerning the decisions on price and reimbursement of medicines. The main objectives of this proposal are to improve its functioning and effectiveness by updating this regulatory instrument in the light of

- the evolution of the pharmaceutical market,
- the results of the Pharmaceutical Sector Inquiry of 2009
- the extensive interpretation of the European Court of Justice delivered in the last 20 years
- the significant disparities and the frequent excessive delays regarding pricing and reimbursement decisions in Member States.

[29] EU legislation may address such issues, for example Article 46b(4) of Directive 2011/62/EU amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products introduces provisions for facilitating the importing of active substances to ensure the availability of medicinal products. The possible impact of this measure should be further investigated.

looks into any drivers of unavailability of medicinal products. For instance, one would expect that in any decision concerning supply, potential costs or time associated with obtaining marketing authorisations would be set against the size of the market, likely pricing and reimbursement outcomes, the perceived demand, and expected margins. A producer may decide not to seek authorisation or not to market a product in a specific Member State if costs of authorisation are seen as disproportionately high when compared to potential revenues. The figure below outlines some of the main drivers and the ways in which they are interrelated, focusing on the interplay between regulatory system and corporate drivers.

Figure 16: Problem drivers



The sections below outline the potential drivers based on the research conducted, and structured according to different stages in the process of bringing medicinal products to the market.

5.1 Marketing Authorisation

Already at this point in the process, when seeking authorisation through national procedure or an EU-wide authorisation, the producer can decide not to market the product on some national markets. The producer may deem a particular market too small, and decide that it is simply not **profitable** to seek authorisation for a product in that particular Member State. This constitutes unavailability because that particular medicinal product would, at least initially, not be available in a given market.

The size of the market and unwillingness of producers to authorise products in these markets has been noted by stakeholders in smaller Member States, such as Latvia and Cyprus. The interviewees also pointed out the fact that some marketing authorisation holders (MAHs) do not have local offices in these Member States, which they see as a problem driver. According to the interviewed stakeholders, lack of local presence results in producers having limited understanding of the situation and needs in a given market and makes them less likely to introduce certain products in these markets. It is however likely that the decision not to open local offices in these markets can also be linked to the perceived market size.

In addition, potential **language requirements** in these markets (and also in larger markets with multiple official languages, such as Belgium) and the costs associated with them are seen by consulted NCAs as a reason why producers are more likely to decide not to authorise the product in a given market.

There are also specific issues related to particular types of products. Stakeholders in the self-medication industry note that differences in attitudes to **OTC** products in individual Member States may result in the application to switch a product's status from prescription to OTC as being difficult and time consuming, if not ultimately rejected. Similarly, these stakeholders also identify similar national differences with regard to authorising **herbal medicinal products**. In both cases this can result in limited availability of such products as medicinal products in pharmacy settings. In the field of **HAMPs**, lack of a coherent legal framework across the EU that would allow for products to be authorised (both new products and those already on the market) is also seen as an important driver of availability problems.

Finally, as mentioned in the previous section, the incorrect linking of **authorisation procedures and intellectual property (IP) issues** in some Member States means that authorisation of generic products can be effectively blocked until a potential patent infringement dispute is resolved. It is however worth noting that these problems were limited to only a small number of Member States. According to stakeholders consulted, these issues were initially present in Italy and Portugal. Since then, Italy has adjusted its legal framework and so has Portugal, although in the latter case the relevant national legislation now includes arbitration procedure, which can effectively result in similar delays.

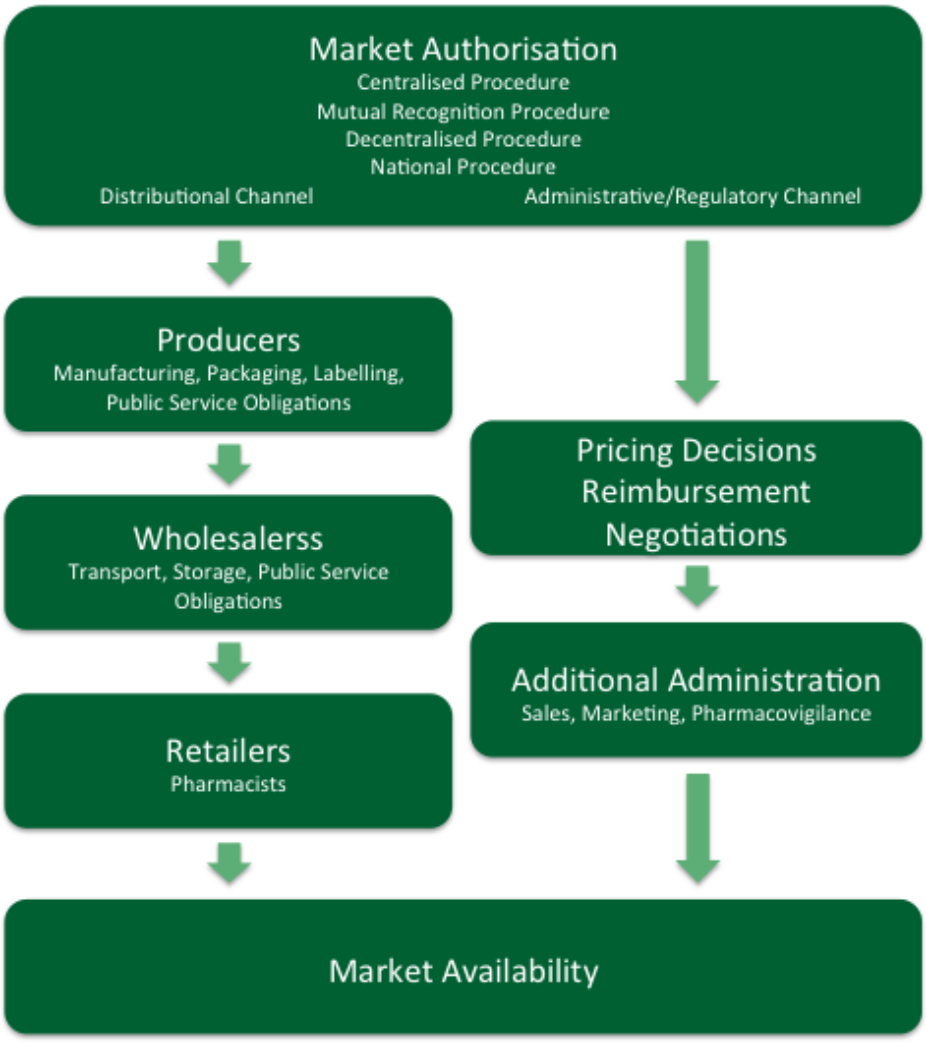
Another aspect of authorisation problem drivers mentioned by stakeholders and discussed in the HMA report[30] is **dossier upgrading.** Although the purpose of dossier upgrading was to ensure the good quality, safety and efficacy of medicines available in the EU and therefore safeguarding public health, it sometimes resulted in businesses withdrawing products from the markets of accession Member States rather than attaining a new marketing authorisation. Stakeholders both in Cyprus and Malta noted that, at the time of accession in 2004, dossier upgrading was a serious problem with Cyprus being left with approximately 10% of existing authorisations after EU accession. In Malta 17% of authorisations in place prior to EU accession remained. Competent authorities both in Malta and Cyprus have followed different strategies to address the unavailability of medicinal products. These strategies include for example the

[30] Heads of Medicines Agencies (2007), 'Availability of Human Medicinal Products – Report of Task Force of HMA MG', http://www.hma.eu/.../Availability_medicines_HMAMG_TF_Report.pdf

reduction of relevant costs associated with authorisation of products (in Malta) or the introduction of products using Article 126a of Directive 2001/83 EC (Cyprus Clause). It is however important to note that Article 126a, which is discussed in more detail in the next section of the report as well as in one of the case studies, is used less frequently in other small markets.

Following the market authorisation, the route to market follows two individual channels, as shown in the figure below.

Figure 17: Administrative and distributional steps to introducing a medicinal product to a national market



It is important to note that the above figure represents a simplified view of the process with some elements being ongoing processes starting with marketing authorisation.

At this stage, the differences between placing on the market of generic medicinal products compared to originators should also be noted. For instance, there are differences in the marketing authorisation process in EU legislation for generics since they need to meet fewer

requirements than originators. Generic competition should be available immediately after expiry of the patent term. However, market entry for generic medicinal products following the expiry of the main basic patent in all EU markets can still be difficult and is very often delayed[31]. Due to a diminishing number of newly registered products and contracting product pipelines, originator producers may aim to prolong the patent monopoly of existing products. This is known as the '**evergreening'** of a basic patent with the help of follow-on patents[32]. Although evergreening would not affect the availability of the originator product, it would lead to a delay in the placing on the market of generic substitutes and as a result it would affect the availability of lower-cost generic products. However, focusing on the availability of active substances and disregarding issues of affordability or access, the public health implications of such delays would be limited as long as originator products are available on the market.

5.2 Administrative Channel

Once authorisation is obtained, producers make **pricing decisions** for the national market and engage in **reimbursement negotiations** of their prescription products with national authorities. Pricing and reimbursement procedures can have an impact on availability of products in two ways:

- Outcomes of pricing and reimbursement procedures can influence the manufacturers' decision whether a given product will be marketed in a Member State in question. A UK stakeholder noted even that in large markets such as the UK, pricing and reimbursement outcomes are likely to be the main reason behind products not being marketed.
- Procedures may be time-consuming and may require sizable upfront investments, potentially resulting in products being available on the market with a delay.

Since pricing and reimbursement is an area of Member State competence (regulated to some extent by the Transparency Directive 89/105/EEC), the outcomes of the procedures and any resulting time delays in bringing products onto the market will be dependent on the exact nature of Member State pricing and reimbursement policies and procedures and, as a result, the availability implications of pricing and reimbursement procedures will differ across Member States.

For instance, some, but not all, Member States carry out assessments of clinical performance, economic evaluations, or compare the product in question to the cost of existing treatments as part of the pricing and reimbursement process[33]. All of these practices will have an impact on the outcome of the pricing and reimbursement procedures, as well as on the time taken to bring the product onto the market.

[31] As noted in the Pharmaceutical Sector Inquiry Report, available at: http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/
[32] Roox et al. 2008
[33] See http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/

Because reimbursement negotiations often adopt the principle of **External Price Referencing (EPR)**, where the price paid for a product in other Member States is taken as a guide, there may be an incentive for manufacturers to avoid introducing medicinal products to markets where a low price may prevail, because this may push prices down in other countries too.[34] In addition, lower prices may make the market less attractive in general. An example of this, according to the stakeholder consultation, is Slovakia where low prices are seen as a source of unavailability problems. A stakeholder from the Netherlands noted that a reverse effect is also possible, where products are registered in order to steer reimbursement prices, but are not marketed. Consulted stakeholders noted that, more generally, pricing and reimbursement procedures will always play a role in the corporate decision whether to introduce the product into the market, and expected pricing and reimbursement outcomes can have an impact on manufacturer's decisions even prior to or after authorisation.

External Price Referencing

External Price Referencing (EPR) is defined as "The practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country."[35].

The practice is also known as External Price Benchmarking (EPB) or International Reference Pricing (IRP) and involves the selection of a basket of countries, which can change over time, to compare pharmaceutical prices and create the reference price for the country in question[36]. There are different types of ERP with varying combinations of methods for choosing or calculating it and there are also many ways to apply ERP in practice[37].

The methods for calculating the external reference prices can vary in several aspects. Factors to be considered are:

- the criteria used to choose the basket of reference countries, including the adequacy of the regulatory system;
- the number and specific set of countries used as references;
- the date of the price in the reference countries (e.g. current price vs. price at launch); and
- the selection or calculation of the reference price (lowest price in the set, simple average of all products, weighted average, etc).

The resulting figure may, for example, be adjusted by a specific parameter to adjust to the lower economic capacity of the country relative to the reference countries. The reference price can be

[34] More information available at: http://www.europarl.europa.eu/activities/committees/studies/download.do?language=en&file=35108
[35] WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies (WHOCC) Glossary of Preferred Terms. Available at: http://whocc.goeg.at/Glossary/Search
[36] Kanavos, P. et al (2010), 'Short- and Long-Term Effects of Value-Based Pricing vs. External Price Referencing' http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/valuebased_pharmapricing_012010_en.pdf
[37] Espin, J. et al (2011), WHO/HAI Project on Medicine Prices and Availability. Working Paper 1: External Reference Pricing' http://www.haiweb.org/medicineprices/24072012/ERPfinalMay2011.pdf

enforced as a condition to either authorise the marketing of the product in the country, or, more commonly, as a condition for the health system's coverage and reimbursement[38].

Finally, the external reference prices based on prices of other countries may be used as the only mechanism to establish or negotiate pharmaceutical prices or it can be used in combination with other methods such as cost-plus methods (by which price is based on the cost of production with a profit margin plus supply chain charges), internal or therapeutic reference pricing (which entail the use of the price(s) of identical medicines (ATC 5 level) or similar products (ATC 4 level) or even with therapeutic equivalent treatment (not necessarily a medicine) in a country in order to derive a benchmark or reference price)[39].

Potential **time delays** resulting from the pricing and reimbursement procedure can be very long and thus effectively constitute temporary unavailability compared to countries where these time delays are shorter. One of the consulted stakeholders noted this to be particularly problematic with regard to vaccines. In addition, a stakeholder noted that in Italy individual regions are responsible for implementing pricing and reimbursement decisions taken on national level, which can in turn result in additional delays.

Once pricing and reimbursement decisions have been made, the producer generally incurs **additional administrative costs** of maintaining a product on the market. Finally the **upfront national fees** associated with reimbursement negotiations may prove prohibitively high if it is too complicated a procedure and may ensue in significant delays in availability. However it has been established that, in general, costs of regulatory procedures do not significantly influence decisions on authorisation[40]. There is little comparative data on the specific administrative fees charged by competent authorities for pricing and reimbursement applications. For instance, in Poland, administrative fees currently vary between about EUR 50-100 though there are plans to raise rates to EUR 2,250 for a reimbursement application. In France, fees are EUR 2,875 for a first time application for reimbursement, EUR 1,725 for a renewal and EUR 575 for an application for a modification. Finally, differing **value added tax** (VAT) rates on pharmaceuticals across Member States might also affect prices and profit margins.[41]

It is important to note that the above factors are not directly dependent on the size of individual Member States. If they can be shown to have an impact on availability, it would therefore appear that, although they will be weighed against the size of the market by the producers, **the availability problem is not exclusively a problem of small countries,** which is also in line with the findings of previous sections focusing on authorisation[42].

[38] See: http://www.haiweb.org/medicineprices/24072012/ERPfinalMay2011.pdf
[39] Heads of Medicines Agencies (2007), 'Availability of Human Medicinal Products – Report of Task Force of HMA MG', http://www.hma.eu/.../Availability_medicines_HMAMG_TF_Report.pdf
[40] Heads of Medicines Agencies (2007), 'Availability of Human Medicinal Products – Report of Task Force of HMA MG', http://www.hma.eu/.../Availability_medicines_HMAMG_TF_Report.pdf
[41] See: http://www.europarl.europa.eu/activities/committees/studies/download.do?language=en&file=35108
[42] See http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/1_Estonia_AvailabilityHumanMedicinalProducts-Europe.pdf

Although important to the issue of availability of medicinal products, these drivers are not the central focus of the analytical part of the study, since they do not relate directly to the authorisation process. Nevertheless, it is worth considering them in order to obtain a full picture of the availability problem and its drivers, which will help develop conclusions with regard to potential actions in the regulatory arena. In addition, some of the European provisions are of relevance also to availability of medicinal products after they have been authorised, which means that conclusions drawn from investigating these factors are of relevance to the potential review of the pharmaceutical *acquis*. One key finding is that the size and importance of these regulatory drivers is likely to differ across the Member States. At the same time, according to the interviews, in Member States most affected by unavailability problems, such as Malta, a number of steps were already taken to reduce some of the potential regulatory obstacles to availability. This in turn suggests that, although changes in the area could aid availability, in the Member States where the problems are most acute, the room for manoeuvre is likely to be limited.

5.3 Distributional Channel

In addition to problems associated with the regulatory and administrative aspects of introducing a medicinal product onto a national market, the dynamics of the supply chain can also result in availability problems. For example:

- Disruptions and problems associated with the manufacturing of a product can be linked to changing trends in the global supply chain. An Austrian stakeholder noted that an increasing **dependency on a limited number of manufacturing sites**, especially outside the EU, can mean that a potentially minor unexpected disruption can have substantial impact on availability.
- Good Manufacturing Practices (GMP) compliance problems may also cause supply shortages. This issue has been considered in the EMA's Incident Management Plan for medicines for human use[43].
- Being a small country with a **unique language** may create additional costs to producers in terms of **packaging and labelling**, and may make providing a product economically unviable, since the cost of introducing a product in that market would need to be justified to the headquarters of manufacturer in question. Language and labelling issues have been identified as a problem driver in a number of Member States, in particular Cyprus, Belgium (where there are three official languages) and Iceland, as well as being noted in the HMA report[44].
- Small markets restrict wholesalers' incentives to distribute the product, because limited demand means that **small quantities of a product with an expiry date** may be too costly to store and transport, and there may simply not be a large enough breadth of products to distribute for it to be profitable.
- **Ordering and stocking** small quantities of relatively expensive products may also not be desirable for pharmacies.

[43] See http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/07/WC500130379.pdf
[44] Heads of Medicines Agencies (2007), 'Availability of Human Medicinal Products – Report of Task Force of HMA MG', http://www.hma.eu/.../Availability_medicines_HMAMG_TF_Report.pdf

5.4 Parallel Trade

Parallel trade refers to the import of a medicinal product "into one Member State from another and then distributing it outside the distribution network set up by the manufacturer or his/her authorised distributor"[45]. Parallel trade is made possible by price differences across Member States**,** which can in turn have an impact on availability of medicinal products. Stakeholders have noted that:

- in Belgium, despite wholesalers being obliged to first supply the domestic market (via a Public Service Obligation or PSO), there were instances of infringements;
- in Italy prices are generally lower than in other Member States meaning that Italy is an exporting country. This in turn can in rare instances lead to shortages of products.
- in Lithuania there were instances where prices of products were lowered to include them in the reimbursed products lists, which in turn spurred parallel exports and creating availability issues;
- in Norway there were occasions where parallel export was linked to products not being delivered to the customers in due time; and
- in Sweden trade within the country with the aim to parallel export has also lead to disparities in availability between regions.

In the cases outlined above availability problems due to parallel export tended to be occasional problems. According to interviewed stakeholders, this appears to be different in Slovakia and Spain, where lower prices mean that parallel export regularly contributes to shortages.

Finally, an availability issue related to parallel trade is linked to **quotas** discussed in the previous section. For example, in the UK parallel trade by pharmacies is widely seen as the reason why companies impose quotas and supply caps, which in turn lead to availability problems.

It is important to note that parallel trade can also **enhance availability**. In Latvia parallel trade is viewed as a source of products not previously available, as well as a way of bringing down the prices of reference products. This is also the case in Malta, where current requirements for parallel import are seen as contributing to tackle unavailability problems.

5.5 Summary of Problem Drivers

The following table summarises the problem drivers identified, linking them to likely impacts, geographical spread, and EU competences.

[45] See http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/pharmaceutical_and_cosmetic_products/l23110_en.htm

Table 2: Summary of problem drivers

Unavailability problem	Possible Driver	Impact	Geographic spread	Relevant product types	Competence (EU/National) and available instruments
Products not authorised/ not marketed/ withdrawn from market after authorisation	Low profitability of the market due to • lower expected prices (e.g. price controls, external price referencing) • smaller expected market size	Potentially substantial as important pharmaceutical developments may remain unavailable to segments of EU population	EU27 and EEA	All products	Obligation to supply medicinal products when on the market; linking supply to authorisation (Article 81 Directive 2001/83/EC)
Products not authorised/delayed authorisation	Divergence in national procedures and approach to herbal medicinal products and HAMPs	Depends on the demand for herbal products and HAMPs. Potentially moderate if MS with general lower use of such products are the ones where most delays/authorisation issues occur. In addition, Herbal products can be available on the market as, for example, food supplements.	Selected EU27 Member States (i.e. Italy)	Herbal products and HAMPs	Legal framework set out in Article 13 0 Article 16 of Directive 2001/83/EC and in Directive 2004/24/EC on Traditional Herbal Medicinal Products
Products not authorised for use in the paediatric	Perceived costs and ethical issues associated with	Potential risks due to using authorised products or using	EU27	Paediatric products	Obligations and rewards in the Paediatric Regulation 1901/2006

Unavailability problem	Possible Driver	Impact	Geographic spread	Relevant product types	Competence (EU/National) and available instruments
population	clinical trials involving children	products off-label			
Products not marketed/delayed entry to market	Time delays resulting from pricing and reimbursement procedure	Potentially substantial as important pharmaceutical developments may remain unavailable to segments of EU population	Member States experiencing time delays	All products	National competence, however, Transparency Directive (89/105/EEC) sets deadlines for pricing and reimbursement decisions
Products not marketed/delayed entry to market	Costs for pharmaceutical companies due to upfront fees associated with reimbursement negotiations	Potentially substantial as important pharmaceutical developments may remain unavailable to segments of EU population	Member States experiencing time delays and more complex pricing and reimbursement negotiations	All products	Transparency Directive (89/105/EEC) aims to make negotiation processes more transparent
Products not marketed/ delayed entry to market	Costs for pharmaceutical companies due to: • Administrative costs to keep a product in the market • Fees for application for authorisation • Fees for	Potentially substantial as important pharmaceutical developments may remain unavailable to segments of EU population	EU27	All products	Competence over pharmacovigilance fees for centrally authorised products and some EU procedures involving nationally authorised products, administrative costs, or VAT rates Commission Regulation (EC) No 2049/2005 introduces provisions for

Unavailability problem	Possible Driver	Impact	Geographic spread	Relevant product types	Competence (EU/National) and available instruments
	pharmacovigilance obligations • Higher VAT rates in some MS Costs are likely to be relatively higher for smaller businesses				fee reductions, exemptions, and deferrals and sets up an administrative assistance system aimed at SMEs
Products removed from markets	Dossier upgrading	Substantial as it can lead to a number of products being removed from the market within a short period of time	E.g. Malta, but could be a common problem in newer MS	All products	Mechanisms to place products on the market justified public health reasons in the absence of authorisation (Article 126a of Directive 2001/83/EC)
Products not marketed	Language labelling requirements, especially in smaller markets	Potentially substantial as important pharmaceutical developments may remain unavailable to segments of EU population	Small national markets with a unique language, multilingual countries	All products	Possibility for companies to produce multi-lingual packs for multiple (small) national markets (Article 63 of Directive EC/2001/83)
Products not marketed	Transport and wholesaling problems for: • Products with low frequency of ordering	Potentially substantial as important pharmaceutical developments may remain unavailable to segments of EU	Smaller markets such as Malta, Cyprus and Iceland	All products	Limited competence

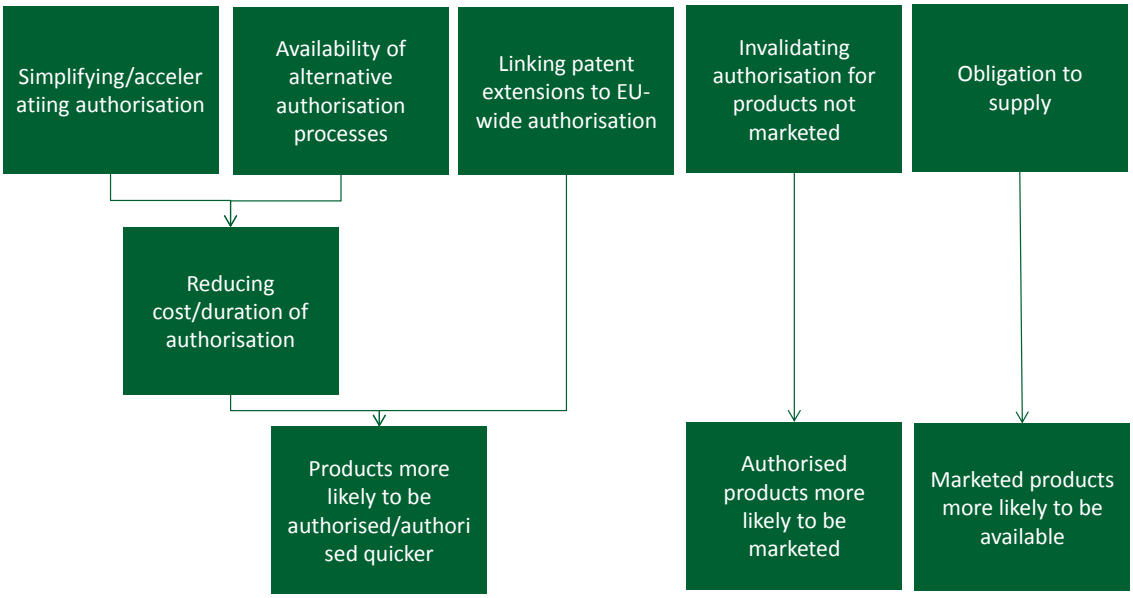
Unavailability problem	Possible Driver	Impact	Geographic spread	Relevant product types	Competence (EU/National) and available instruments
	• Higher transport costs to small distant markets	population			
Generic products not marketed	Costs issues associated with packaging, transport, and wholesaling, as well as requirements of Directive 2011/62/EU on falsified medicines	Can lead to reduced availability of generic products where margins are too low. Public health impact partially mitigated if originator products are available.	EU27 + EEA	Generics	Limited competence with regard to transport and wholesaling costs Directive 2011/62/EU allows for exemption from some GMP (good manufacturing practice) requirements to aid availability
Orphan medicines Products not marketed	Cost issues and reimbursement of orphan medicinal products	Potentially substantial as there are more over 5,000 orphan diseases in Europe	EU27	Orphan medicines	Possibility to exclude medicinal products from authorisation requirements in specific individual circumstances (Article 5(1) of Directive 2001/83/EC) Regulation (EC) No 141/2000 (supplemented by Regulation (EC) No 847/2000) aims at introducing incentives to ensure availability of orphan products
Delayed authorisation of generic medicinal	Incorrect linking of authorisation and IP procedure resulting	Moderate since it occurs in only a few markets	Portugal (previously also Italy)	Generics	Could be seen as an incorrect implementation of regulatory framework

Unavailability problem	Possible Driver	Impact	Geographic spread	Relevant product types	Competence (EU/National) and available instruments
products	in delays in authorisation				concerning marketing authorisation (as set out in Directive 2001/83/EC)
Delayed market entry for generic medicinal products	“Evergreening” of basic patent with the help of follow-on patents	Can lead to unstable supply of lower priced medicines. Public health impact mitigated in part if originator products are available.	EU27	Generics	Limited, except where there are mechanisms in place so patents be withdrawn or extended to secure availability (e.g. Regulation (EC) No 1901/2006) EU Competence in ensuring free competition and free movement of goods in the internal market
Disruptions in supply of authorised and marketed products	Small number of manufacturing sites and a global supply chain are prone to disruption which can restrict supply	Potentially substantial, given that manufacturing sites may require substantial amount of time to restart	EU 27	All products, but primarily higher priced products produced in smaller quantities	Directive 2011/62/EU allows for exemption from some GMP (good manufacturing practice) requirements to aid availability
Disruptions in supply of authorised and marketed products	Shortages linked to quotas and parallel export	Potentially substantial	EU27 (primarily parallel export countries)	All products	Obligation to supply medicinal products when on the market; linking supply to authorisation (Article 81 Directive 2001/83/EC)

6.0 Impact of Existing Measures (WP3)

This section focuses on the relationship between existing EU pharmaceutical *acquis* and the availability of medicinal products. Although EU legislation deals first and foremost with safety, efficacy and quality of medicinal products, the European Union has, for a number of years, been targeting the problem of limited availability of medicinal products, at least, in a peripheral way. In this context, several provisions have been passed concerned (partially or wholly) with tackling this issue.[46] The figure below outlines our understanding of the conceptual relationship between the EU legislation and unavailability.

Figure 18: Impact of EU pharmaceutical legislation including obligation to supply products put on the market



Significant changes introduced by recent pharmaceutical legislation with a bearing on availability can be summarised in the following issues:

- obligation of continuous supply of products
- allowing for alternative ways of bringing a product to a market bypassing the regular authorisation procedure in specific situations
- encouraging EU-wide authorisation of products and allowing for more flexible use of the centralised procedure
- encouraging the marketing of authorised products
- granting labelling exceptions
- keeping national competent authorities well informed about any potential unavailability issues; and
- regulating sales at a distance.

[46] ToR

6.1 Existing EU Pharmaceutical Legislation

As noted in the previous sections, the EU has limited competence in the area of medicinal products. The EU legislation in this area focuses on the European authorisation procedures and in particular the safety, quality and efficacy of the process. However, selected legal provisions are of relevance to availability. The list of provisions having a bearing on availability is reported in Table 3 below.

The table includes provisions identified through legislation screening and stakeholder consultation (in bold) as well as the provisions already identified in the ToR. The focus is on EU legal provisions already in place and applicable prior to July 2012. Therefore, amendments of Directive 2001/83/EC as per Directive 2010/84/EU and Directive 2011/62/EU[47] have been listed in the table below but have not been discussed with stakeholders as they did not have enough perspective to analyse their impact.

Table 3: Relevant articles in EU legislation having a bearing on availability of medicinal products

Relevant articles in EU legislation	Reasons for inclusion
Directive 2001/83/EC on the Community code relating to medicinal products for human use[48]	

[47] The deadline for transposition in Member States of the latest amendments of Directive 2001/83/EC as per Directive 2010/84/EU was 21 July 2012 and as per Directive 2011/62/EU is 2 January 2013. More information available at: http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/pharmaceutical_and_cosmetic_products/l21230_en.htm

[48] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Consolidated version : 05/10/2009).

Relevant articles in EU legislation	Reasons for inclusion
Article 5(1)	This article authorises healthcare professionals to prescribe, under their direct personal responsibilities and in accordance with legislation in force, medicinal products that have not been authorised in national territories to individual patients to fulfil special needs. Thus, this article allows for an alternative way of bringing products into a market where it is needed but is unavailable.
Article 10(1)	This article also allows for an alternative way of bringing products into a market where it is needed but is unavailable. It introduces the possibility of authorising a generic medicinal product in a Member State in the absence of a reference medicinal product in that Member State by relying on a reference product in another country.
Article 10a	By allowing applicants to endorse their application with the appropriate scientific literature to demonstrate the well-established use of active substances instead of test and trial results, this article may facilitate the authorisation of a medicinal product and its placement in the market.
Article 23a	This article ensures that competent authorities have accurate and up to date information on whether authorised medicinal products have been actually placed in the market and therefore are available to patients or whether such products have ceased to be placed in the market and become unavailable.
Article 24(4), Article 24(5), and Article 24.6	This article, known as the “Sunset clause”, invalidates the marketing authorisation if the product is not placed on the market for 3 consecutive years or not present on the market for three consecutive years.
Article 46b[49]	To ensure availability of medicinal products, Member States may temporarily waive the requirement of a written confirmation of a number on issues related to good manufacturing practice from the competent authority of the exporting third country. This may happen exceptionally when a plant manufacturing an active substance for export has been inspected by a Member State and was found to comply with the principles and guidelines of good manufacturing practice (Art. 47).
Article 63(1)	This article allows marketing authorisation holders to place products in the market with multilingual packages, provided that the same information appears in all the languages used. In the case of orphan medicines, the provision also allows marketing authorisation holders to place a product in the market provided that the information on the products appears in at least

[49] As amended by Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products. This amendment has entered into force on 21 July 2011 and the deadline for transposition in Member States is 2 January 2013.

Relevant articles in EU legislation	Reasons for inclusion
	one of the official languages of the Community.
Article 63(3)[50]	When there are severe availability problems or the product is not to be delivered directly to patients, competent authorities may grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet and they may grant a full or partial exemption to the obligation that the labelling and the package leaflet must be in the official language or languages of the Member State in question.
Article 81	The second subparagraph of this article implores the holders of marketing authorisation and distributors of medicinal products actually placed on the market to, within the limits of their responsibilities, ensure appropriate and continued supplies of the product to cover the needs of patients in the Member State in question.
Article 85c[51]	This article regulates sales at a distance. It may have a greater bearing in terms of access to medicinal products than in terms of availability but it may also help reduce unavailability of medicinal products by facilitating distribution and management of stocks and potentially reducing delays to get medicines to patients.
Article 126a	In the absence of a marketing authorisation or of a pending application for a medicinal product, this article, known as the "Cyprus clause", allows a Member State to authorise in justified public health reasons the placing on the market in its territory of a medicinal product authorised in another Member State. Member States should inform the Commission when they avail themselves of this provision and the Commission publishes a list of the medicinal products concerned. According to this list, the provision has been used over 900 times by Cyprus, four times by Poland and once by Lithuania (it is worth noting that the use by Malta is not included in the list). The article has been amended by Directive 2010/84/EC to make the procedure even more flexible. The Article can only be used for products complying with the EU pharmaceutical *acquis*.
Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines	

[50] Art. 63.3 as amended by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. (Official Journal L 348, 31/12/2010, p. 74 - 99). This amendment has entered into force on 20 January 2011 and the deadline for transposition in Member States was 21 July 2012.

[51] As amended by Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products. This amendment has entered into force on 21 July 2011 and the deadline for transposition in Member States is 2 January 2013

Relevant articles in EU legislation	Reasons for inclusion
Article 3	Article 3 sets out the products for which a centralised marketing authorisation procedure is compulsory. They include orphan products, products developed using biotechnology processes, and products for which the therapeutic indication is the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorder, diabetes, auto-immune diseases and other immune dysfunctions, and viral diseases.
(Article 13(4))	(Same provision as Article 23a of Directive 2001/83/EC)
(Article 14(4), Article 14(5) Article 14(6))	(Same provision as Articles 24(4), 24(5) and 24(6) (Sunset clause) of Directive 2001/83/EC).
Article 14(7)	This provision allows the European Commission to grant conditional marketing authorisations. Conditional marketing authorisations are also regulated in Commission Regulation 507/2006.
Article 14(9)	This provision allows applicants to request accelerated assessments for medicinal products that are of major interest a public health perspective, especially in terms of therapeutic innovation.
Article 82(1)	Applicants are allowed to submit more than one application to the Agency for a medicinal product when there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health-care professionals and/or patients.
Article 83	Member States may make medicinal products available for compassionate use.
Consolidated version of the **Council Regulation (EC) No 297/95** on fees payable to the European Agency for the Evaluation of Medicinal Products	
Article 9	According to this article, a total or partial exemption from payment of fees may be granted for medicinal products for public health reasons, for medicinal products for treating rare diseases or for medicinal products available for compassionate use.
Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products	
Article 7(3)	Through this provision, a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if, among other things, the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the product.
Article 9	Incentives to support research into, and the development and availability of, orphan medicinal products.

Relevant articles in EU legislation	Reasons for inclusion
Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council	
Article 4(1) (c) and (d)	This regulation deals with conditional authorisation for medicinal products. Article 4(1)(c) and (d) specifically indicates that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, a conditional authorisation may be granted when, among other things, unmet medical needs will be fulfilled and the benefit to public health of the immediate availability on the market of the medicinal product outweighs the risk inherent in the fact that additional data are still required.
Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use	
Article 33	In the case of products that have already been marketed with other indications, the marketing authorisation holder shall place a product on the market taking into account the paediatric indication within two years of the date on which the paediatric indication is authorised.
Article 35	This article prevents products with paediatric indications to be discontinued by allowing a marketing authorisation to be transferred to an interested third party (when the marketing authorisation holder has benefited from rewards or incentives under Article 36, 37 or 38, and these periods of protection have expired).
Article 36(3)	This provision offers the incentive of an extension of the supplementary protection certificate (essentially a patent extension) only if a product is being marketed in all Member States.
Articles 37, 38 and 39	Incentives and rewards regime for products with paediatric indications, including incentives to support research into, and the development and availability of, medicinal products for paediatric use (Art 39).

6.2 Impact of EU Pharmaceutical Legislation

The stakeholder consultation and in-depth case study interviews focused on the awareness, use, and views concerning specific elements of the EU pharmaceutical *acquis*.

Stakeholders consulted were generally well aware of EU legislation but, to them, the impact of existing initiatives on the availability of medical products is sometimes mixed. Some provisions are considered to be more helpful than others, depending on the particular circumstances of the Member State (i.e. smaller vs. larger markets, singularity vs. plurality of languages). In terms of the efforts to address unavailability problems through EU legislation, even if this is not a central

aim of the existing legislation, some of them considered it to be very helpful, but also indicated that more could be done at European level, for example some amendments to further facilitate the authorisation of medicinal products. Stakeholders also recognised that much of what can be done to avoid shortages of products is still in the industry's hands.

Table 4 below summarises stakeholders' comments on some the provisions identified in the previous section.

Table 4: Impact of EU legislation according to stakeholders

Relevant articles in EU legislation	Relevance to availability and impact
Directive 2001/83/EC	
Article 5(1)	• Comments from stakeholders about the use of this article are mixed. • Article 5(1) is commonly used and considered important in some Member States (e.g. Estonia, the Netherlands, and Cyprus). To them Art. 5(1) is at the moment the only possibility to solve availability problems and "is a life saver article". Stakeholders have expressed a preference to keep the article unchanged. • Stakeholders have mentioned that to solve availability problems, it is often better to use article 5(1) than article 126a, as the proceedings described in Art. 126a should be started by a company that will have to import the product and adapt the labelling and packaging. As these procedures are time consuming when the product is needed immediately, it is usually quicker to bring it into the MS using Art. 5(1). • Stakeholders also believe that no company will use Art. 126a if the product is needed by a very limited number of patients (e.g. 5 or 10 patients) and therefore Article 5(1) is more effectively applied in these situations. • However, some stakeholders have noted that Art. 5(1) is not used at all in some Member States (e.g. Austria) while others use their own national provisions addressing this issue. • For example, Spanish legislation allows prescribing medicinal products for special use. There are currently 300 products (many authorised in Europe but not available in Spain) that the State buys and makes available to patients with a prescription. • A suggestion was made to extend/change the scope of the provision to cover a group of patients suffering from a condition instead of using it for individual cases. This way, if healthcare professional anticipate a demand for a specific disease (e.g. malaria), medicinal products can be ordered for multiple and potential patients, avoiding the repetition of the procedure and untreated patients.

Relevant articles in EU legislation	Relevance to availability and impact
	• Finally stakeholders from some Member States have suggested that placing all responsibility relating to the use of the product on the physician who is prescribing the product may deter the use of this tool in some MS.
Article 10(1)	• Only one NCA had any specific comments about the use of Art. 10 to help solving unavailability problems. According to this stakeholder, Art. 10 facilitates authorisation but cannot compel a company to market its products. Nevertheless, the stakeholder noted that they are in favour of the article. • Stakeholders from the industry have pointed out that in spite of Article 10(1), generic companies very rarely succeed in registering a generic medicine when there is no reference product in a Member State.
Article 24(4), Article 24(5), and Article 24(6)	• According to stakeholders consulted, Art. 24(4), 24(5) and 24(6) have little positive effect on availability. • Several Member States consider it to be more helpful to keep authorisations valid even when companies fail to place the products onto a market since a need for the product could arise in the future. According to stakeholders, it could be counterproductive to withdraw the authorisation of medicinal products especially of products that are meant for rare diseases. • While some Member States consider Art. 24 to be useful as a means for incentivising/penalising companies and for remove old and unnecessary authorisations, to others it only makes it easier for companies to lose the authorisation for products they are no longer interested in marketing. • Other stakeholders have noted that the clause helps organise the market but is not so helpful in dealing with availability as it is applied differently in different Member Statss: to some countries it is only valid the first three years after authorisation while to others it is valid all the time and is applicable every time a medicinal product is not supplied for three consecutive years. • Industry stakeholders have indicated that the Sunset Clause is implemented differently in different MS. While some countries automatically cancel Marketing Authorisations, others like the Netherlands leave it up to the MAH to cancel. • As did several NCAs, industry stakeholders have also noted that, on occasions, MAs are lost in some markets when it is no longer economically viable to supply the product. The disadvantage is that if the situation changes or there is a shortage, there is no option to come back to the market quickly.

Relevant articles in EU legislation	Relevance to availability and impact
	Data from individual NCAs appears to confirm some of the stakeholder views regarding the Sunset Clause. For example, Information published by Czech and Finnish NCAs show that respectively 183 and 13 authorisations have ceased to be valid as a result of the sunset Clause[52]. Although taking into account pack and dosage variations these correspond to only a small number of unique products (15 and 8 respectively) they do appear to confirm the concerns of some NCAs that the Sunset Clause can effectively reduce the number of authorised products.
Article 63(1)	• Several stakeholders consulted have indicated that harmonisation, simplification and a more pragmatic approach in labelling and packaging should not be difficult to achieve and could be of great help in improving availability of certain medicinal products. • It was suggested, for example, that more countries could allow English texts or a fairly similar language to the one spoken in the Member State, e.g. products with information in Norwegian or Danish could be marketed in Sweden or products with information in Swedish could be marketed in Norway and Denmark. • Another suggestion is to differentiate what information on a product is absolutely necessary from the information that is good to have but is not essential. Minimising the amount of information that needs to be included in the package could save space to include information in more languages and market the product in more countries. Additional information on the product could be available online. • EMA is currently consulting stakeholders concerning the inclusion of additional languages or new combination of languages in packages. If this was done, Member States with shortages could for example accept more languages or larger Member States could accept to include additional languages in their packaging (e.g. France allowing Czech and Hungarian in labelling).
Article 81	• One stakeholder indicated that Art. 81 is used and exists in their national legislation. The stakeholder however questioned the extent to which one can “implore” wholesalers to supply the domestic market while at the same time not jeopardising the EU internal market.

[52] See http://www.fimea.fi/license_holders/marketing_authorisations/sunset_clause and http://www.sukl.eu/medicines/medicinal-products-whose-marketing-authorisation-has-ceased

Relevant articles in EU legislation	Relevance to availability and impact
Article 126a	• According to stakeholders, in smaller markets like Cyprus and Malta, Article 126a is widely used and the provision should be left intact. The use of the Cyprus clause may be easier for these Member States because, due to language use, British and Irish products may be brought to Malta, while Greek products to Cyprus. Stakeholders in smaller markets noted that they could eventually stop using this provision if, for example, Mutual Recognition procedure would include all Member states. • Other smaller Member States do not rely on Art 126a to address unavailability problems. The main reason given being safety issues linked to the use of the provision, as national authorities may not know enough about the medicinal product in question. Instead, these Member States rely on other approaches, for example, on proactively contacting manufacturers to increase availability. It is an approach they consider to be working. • Some larger Member States have also mentioned they would welcome more clarity around the use of the Cyprus clause as it supplies mechanisms that they consider difficult to enforce. According to one stakeholder, this provision leaves several interpretations up to Member States, but exposes the Member State to the possibility of court cases due to interpretation. • A temporary solution that has been taken up by Member States when there have been shortages of one product was to contact the manufacturer's headquarters to bring into the country all the extra stock they had in other Member States. The product then went to inspection by competent authorities and a patient leaflet was included.
Regulation (EC) No 726/2004	
Article 83	• Most stakeholders have indicated that there are initiatives in their countries to make medicinal products for compassionate use available. • One stakeholder considered that Article 83 is a very complex procedure and is not used very often. Even if the Committee for Medicinal Products for Human Use (CHMP) advises on the programme, it is still up to the NCA to guarantee that such a programme will be acceptable. In the Member States in question only in three occasions has the committee advised on compassionate use programme.

More generally, the consulted stakeholders provided comments concerning possible improvements in existing legislation or EU-level solutions to improve availability of medicinal

products for human use. These are varied and there is no single improvement or solution that was proposed by a majority of stakeholders.

A number of stakeholders identified areas for improvement with regard to the use of MRP/DCP procedures. The specific recommendations are as follows:

- **Mutual Recognition Procedure** could be further simplified. A possible way forward could be to centralise pre-marketing or not to charge any fees for voluntarily automatic or repeat MRP. When extending a license, fees could be reduced. This would allow a duplication of the MA in the CMS with minimum involvement of the RMS. Such a change in the procedure could be helpful in minimising bureaucracy for the RMS and potentially reducing the costs for the MAH willing to authorise their products in other MS, especially smaller markets.
- the use of an **Automatic Mutual Recognition Procedure** as a routine approach to authorising products in small markets was also suggested. Medicinal products could be approved by accepting the dossier without further assessment to the one approved by the RMS.
- Another suggestion is to create a new variant of **Repeat Use MRP** which would allow adding one or several countries via a purely administrative pathway without involving the RMS, under the condition that the product is already authorised in the majority of EU countries.
- It could be also helpful to simplify the **Repeat Use MPR** procedure to allow a rapid reaction to patients' needs. "Zero days" MRP procedure used in Iceland and Cyprus, could be an example to follow[53]. According to stakeholders, it could be particularly relevant for essential products authorised some time previously (e.g. 20-30 years ago) in some Member States but missing in small Member States with very low market potential. It may also be an efficient procedure to react quickly in case of shortages.
- There could be also more **flexibility around the Decentralised Procedure** when including additional MS (e.g. small Member State) during the ongoing DCP procedure. The new CMS could recognise the assessment performed by the RMS and already involved CMSs, without raising additional questions.
- In terms of the **Centralised Procedure (CP)** some revisions may be needed to ensure that new and important products authorised centrally are afterwards marketed in as many Member States as possible. According to one stakeholder, an **obligation to market a product** if it is needed in a particular country should be explored.

Stakeholder consultation has also yielded many recommendations concerning incentives and disincentives aimed at enhancing availability:

[53] Cyprus has introduced a new simplified procedure for accepting applications for the issue of a marketing authorisation for medicinal products for human use, already approved through the MR or DC procedures. This new procedure entails a "Zero Days" application process for the Repeat MRP by which Cyprus has committed to the following: (1) there will be no need for the RMS to update the existing Assessment Report as Assessment Reports from the RMS will be accepted without any comments; (2) no 50 day comments will be submitted thus, practically the application will be approved immediately (Zero Days). The procedure only applies when Cyprus is the only Concerned Member State. Cyprus expects that the agencies acting as RMS to the above procedure may consider charging a lower fee, as the procedure will be of administrative nature only and will not involve an update of the Assessment Report, or any other scientific assessment, and will not affect the Marketing Authorisation already issued in the RMS. More information available at: www.moh.gov.cy

- Stakeholders suggested the introduction of new **regulatory tools to address withdrawal of authorisation** when companies decide to discontinue a product because of, for example, economic reasons.
- Other possible regulatory change to improve availability could be to explore some of the same **legal instruments that seem to be working in the paediatric domain**, for example, extending patent time, provide incentives to circulate products in all MS, etc.
- The use of mechanisms to dissuade companies from making products unavailable, for example through **sanctions and administrative penalties**, was also suggested, although stakeholders also recognised that this might not be the best way to 'encourage' industry.

Other recommendations include:

- Stakeholders in Member States where the price of medicinal products is generally low suggested that there could be a **common pricing policy** in Europe to address the problem of products becoming unavailable due to parallel trade.
- New/more initiatives regarding the **labelling and packaging of medicinal products** were also suggested. These are discussed in more detail later in this section of the report, but these broadly include combined packaging guidelines and multilingual packaging.
- Other mechanisms suggested by stakeholders to solve unavailability problems include **'good practice' agreements** with pharmaceutical companies. These agreements allow health ministries and competent authorities to be informed early when a product is to be discontinued or an authorisation withdrawn.
- Setting up a system of **financial incentives** for making products available could be a lever, according to some of the consulted stakeholders. For example, it was suggested that something should be done to "pamper" and protect old but very useful medicinal products when companies lose interest in producing them. From a regulatory perspective, this could be done by finding mechanisms to encourage small companies to take over the production of this type of products and make them profitable, for example, by offering lower rates to manufacturers.
- In addition to improvements and/or revisions of the current EU legislation, stakeholders have alluded to the potential usefulness of a common EU database including ATC classifications and common guidance introduced by the EMA.
- Stakeholders have also suggested that regulatory authorities could be more transparent in declaring needs for specific medicinal products on the market and work more closely with the industry in preventing availability problems.

6.3 National Initiatives

In our consultation with NCAs, we identified a number of national initiatives aiming at addressing problems of unavailability. These initiatives can be divided into:

- Channels to bring into the country unauthorised products;

- Labelling and packaging initiatives;
- Obligation to supply;
- Initiatives to address discontinuations; and
- Up to date information on unavailability of medicinal products

These are described in more detail below.

Channels to bring into the country unauthorised products onto the market

In the UK, it is possible to bring products without a licence, usually in the case of 'niche' products that are quite specialised. In Ireland there is the batch-specific route (used in the UK as well), allowing for bringing in the product from another European country. In Norway, there are different routes for bringing unauthorised products:

- **Named patient**: this route allows the pharmacy to sell medicines without MA to a specific patient. In order to do that, the prescriber must apply for exemption from MA. Pharmacies may sell the medicine by notifying the NCA in the cases where medicines have marketing authorisation in the EEA, US or countries in PIC/S (Pharmaceutical Inspection Cooperation Scheme)[54].
- For vaccines for humans, immunglobulins and sera, a **specified positive list applies**. In this case, the prescriber applies for exemption from MA individually for each patient. The prescriber sends the application to the pharmacy. The pharmacy checks whether the medicine is on the positive list (as per the above paragraph). If this is the case, the medicine may be sold without delay. The pharmacy then notifies the NCA of the sale of the medicine. If the medicine does not have a MA in the aforementioned countries or is on a specified negative list, the pharmacy must wait for a decision from the NCA prior to selling the medicine.
- **Personal import**: private persons may import medicines for their own personal use. The volume is restricted and the person must be able to document to the Customs that the medicines are for personal use and legally purchased. This is regulated by § 3-2 in Regulation on manufacturing and import of medicinal products.

In Italy, routes unauthorised products to bring products onto the market include:

- **Off-label procedure regulated by Law 648/96.** Law No. 648/1996 provides early access to unapproved medicines when no therapeutic alternative is available on the Italian market, and an innovative medicine is authorised in other Member States, but not in Italy. In the Annex to the law there is a list of pharmaceuticals fully reimbursed by the NHS, including:
    - experimental medicines tested in clinical trial but not yet approved;
    - approved medicines for unapproved uses or indication (off-label use);
    - medicines for the treatment of rare diseases.

[54] PIC/S (Pharmaceutical Inspection Cooperation Scheme) includes Australia, Austria, Belgium, Canada, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Malaysia, The Netherlands, Norway, Portugal, Romania, Singapore, Slovakia, Spain, Sweden, Switzerland and Great Britain) and medicines having MA in countries with Mutual Recognition Agreement (including New Zealand, Australia, Canada and Switzerland)More information available at: http://www.picscheme.org/

The law applies to pharmaceuticals already approved in other countries but not yet in Italy and to pharmaceuticals that have demonstrated clear benefit while "under clinical investigation".

The list of medicines approved for treatment under this law and the approved indication is also published on the Italian Medicines Agency (AIFA) website. A medicine is considered for the inclusion in the 648/96 list following a request to the AIFA Technical Scientific Committee (CTS):

- from physicians specialised in the treatment of the proposed disease;
- from a University or a research centre.

The request needs to be supported by a scientific dossier, which is reviewed by the CTS. The CTS may grant the medicine inclusion on the list for reimbursement under exceptional circumstances and following compelling clinical results. Through inclusion in the 648/96 list, the medicines can be prescribed on an individual basis to patients diagnosed with the specific indication. Beneficiaries may be either former participants in clinical studies or other patients who are diagnosed with indication. The cost of the medicinal products used off-label is reimbursed by the SSN.

- The Decree of the Ministry of Health 11/02/1997 on **"Import regulation of pharmaceuticals not registered in Italy registered in other countries**": the decree regulates the procedure for the import of medicines which are not registered in Italy on the basis of the request of a physician residing in Italy The application is submitted by the physician to the competent Office of Maritime, Air and Border Health of the Ministry of Health (USMAF). The request should contain the following data:
    - the pharmaceutical name and formula;
    - the name of manufacturer or supplier, and of the marketing authorisation holder;
    - the name of the patient and its informed consent
    - a declaration stating that the product is properly authorised in the country of origin;
    - the amount of the product needed, specifying that the therapeutic treatment not exceeds 90 days of therapy;
    - the special need that justifies the use of an unauthorised medicine, in absence of a valid therapeutic alternative; and
    - the statement of the physician to use the pharmaceutical product under his or her own responsibility.

Overall, as mentioned above, these solutions apply to small numbers of products and generally do not appear to be as crucial in ensuring availability as the 'Cyprus clause' outlined in the previous section.

Labelling and packaging initiatives

Common Baltic Package (CBP) Procedure is one approach to addressing labelling issues. Since Baltic States face similar problems of medicines availability, medicines agencies of the three countries (Latvia, Lithuania, and Estonia) have agreed on a common Baltic package procedure and combined requirements of patient information and labelling of packages. The initiative aims at saving resources of stakeholders, making approval of the common Baltic packages easier, smoother, quicker and more transparent. During Common Baltic Package procedure, authorisation holders need to communicate only with one agency (Reference Baltic State) acting on behalf of all three agencies and making a single assessment of applications to proposed changes to an aspect of the labelling or the package leaflet. To use the common Baltic package, the name of the product should be the same in all countries. All requirements from Directive 2001/83/EC as amended and Commission Guideline on the readability of the label and package leaflet of the product shall apply[55].

The CBP is particularly significant, as it could be a potential blueprint for a similar solution in other markets where language and labelling issues have a bearing on availability. However, some of the interviewed stakeholders believe that similarities and close links between the Baltic markets are the reason why the procedure is successful so far and it is not clear if another set of markets could reproduce this. A case study discussing this initiative in more detail will be included in the draft final report.

In addition to the Baltic solution, in Ireland there are solutions allowing repackaging products with availability problems and there is also a significant proportion of products with a joint UK/Irish pack.

Public Service Obligations

One form of an obligation to supply the domestic market is a Public Service Obligation (PSO) placed on pharmaceutical wholesalers. As noted by GIRP, the European Association of Pharmaceutical Wholesalers, PSOs are present in Belgium, France, Finland, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Norway, Portugal, Spain, Sweden and Slovenia. The implication of PSOs is the obligation for wholesalers to supply the domestic market before parallel exporting some of their stock. However, these obligations generally do not place an obligation on manufacturers to supply wholesalers, which is seen as a potential weakness. To explore PSO in more depth and investigate any contradictions with Article 81 of Directive 2001/83/EC, a case study on this issue will be presented in the draft final report.

Discontinued products

In Hungary, when an MA holder intends to discontinue the marketing of a specific medicinal product, the MA holder must notify the wholesalers, the NCA and the health insurance administration agency of the time of delivery of the last production batch of the medicinal product to the wholesaler, at least three months before the scheduled termination. Until the date of termination, the MA holders shall be liable to provide the medicinal product in the quantity required to cover the estimated demand. This procedure is used in Hungary.

[55] See http://www.zva.gov.lv/index.php?id=591&sa=393&top=386

Up to date information on unavailability of medicinal products

In Hungary as well, the NCA shall publish a notice of shortage of a specific medicinal on its website, and shall notify all relevant stakeholders of the shortage. In addition, wholesalers are required to maintain a purchase and inventory management system to ensure the transparency and control of the distribution and supply of medicinal products. The MA holder must also notify the wholesalers, the NCA and the health insurance administration agency when the MA holder is unable to maintain adequate and steady supplies of specific medicinal products resulting in a (potential) shortage of supplies, The MA holder also shall communicate the expected duration of the shortage and the quantity of supplies available during this period. In addition, MA holders shall ensure that wholesalers in Hungary have adequate supplies of medicinal products containing certain types of as defined by the NCA.

Transfer of marketing authorisation

Finally, Hungary also allows for the government to purchase a product license or allow other persons or businesses authorised in a State other than Hungary to engage in the wholesale distribution and/or retail supply of medicinal products when a MA holder of a medicinal product that has received public financing intends to discontinue or is unable to continue the marketing of such product. This is done in cases where being deprived of the medicinal product in question is likely to result in severe or persistent disability for the patients treated with such products; and where there is no other medicinal product with similar active ingredients, pharmaceutical form and strength available in Hungary.

7.0 Conclusions

The study has confirmed that there are availability issues relating to medicinal products experienced across Member States, with smaller states disproportionately impacted. There are three main types of availability problems: products not being authorised, products not being marketed, or authorised and marketed products being unavailable due to shortages and supply disruptions. Engagement with stakeholders suggests that issues relating to authorisation lead to some of these problems, but authorisation is not a dominant factor when set against wider economic factors affecting marketing and distribution of medicinal products.

Secondly, it needs to be stressed that availability problems linked to authorisation are not necessarily linked to an increased public health risk, such a risk being more properly linked to the availability of active substances rather than products per se. Data identified during this study did not allow for a complete analysis of the availability of individual active substances, however the fact that the coverage of ATC codes differs across Member States suggests that the differences in availability of products are likely result in unmet health needs. In addition there was limited feedback from stakeholders concerning availability of specific active substances. Overall, it was not possible to establish that the reduced availability of active substances was directly related to authorisation issues.

The study also found that the EU pharmaceutical legislation in some cases has had a positive impact upon existing authorisation procedures and contributed to increasing the overall availability of products. This has been most successful where the relevant provisions focussed on specific conditions or patient groups e.g. paediatric medicines. It has been less successful where they have attempted to achieve broader impact such as with the Sunset Clause.

Relatively few products are authorised centrally, and whilst the procedure is likely to become a more prevalent form of authorisation over time, efforts should still be made to support a broad range of authorisation procedures and to assess how the interaction between authorisation and availability can be most effectively addressed. As such there is evident scope for improvement in the European pharmaceutical *acquis*. In terms of recommendations there is a need to better understand issues relating to availability as it impacts on public health and most particularly the impact of different policy measures on the availability of a broad range of products and active substances. This in turn will help to focus efforts at future policy amendment or change. Specific recommendations include:

- Remove or revise the Sunset Clause provision to avoid reducing the number of authorisations in place in individual EU Member States
- Further clarify the responsibilities of individual actors when using a Cyprus Clause procedure to make it a viable solution to availability problems for more Member States facing such problems
- Work to improve the national implementation of simplified procedures for herbal medicinal products and HAMPs
- Ensure more effective transposition and implementation of Article 81

Such steps would however not address the substantial economic problem drivers. One potential solution focussed on this issue put forward by some of the NCA stakeholders, is to explore the possibility of using sanctions and rewards to incentivise MAHs to authorise and supply medicinal products in more European markets. The Paediatric Regulation, which awards patent extensions to MAHs authorising products for use in the paediatric population, is considered a potential blueprint. Such system would however need to ensure that products authorised and marketed correspond to the health needs of the EU population and that resulting rewards do not negatively affect market access for lower-priced generic products.

8.0 Appendix I: Case Studies

8.1 Case study 1: Use of Article 126a of Directive 2001/83/EC (Cyprus Clause)

Member states	Cyprus, Malta and Iceland
Information Sources	Interviews with NCAs (mainly Cyprus, Malta, Iceland) Published reports Information provided on respective NCA websites

8.1.1 Background

Smaller markets for medicinal products in Europe are more prone to face availability problems than larger markets. Particularly small markets in the EU/EEA are Iceland, Malta, Luxembourg and Cyprus (less than one million inhabitants). In the case of Cyprus, Iceland and Malta, their insularity and remote location may make availability of certain products even more difficult due to logistical issues. In addition, for Malta and Cyprus, their relatively late accession to the EU (2004) also made availability problematic in the past due to dossier upgrading. It was with the intention of helping addressing availability issues, especially in smaller Member States, that the Commission established through Directive 2004/27/EC and Article 126a a mechanism to place medicinal products onto the market for justified public health reasons.

During the stakeholder consultation phase, it was noted by several interviewees that the provisions in Article 126a of Directive 2001/83/EC (also known as the Cyprus Clause) were regularly used by smaller countries, notably Malta and Cyprus. In contrast, stakeholders in Iceland, a country with comparable characteristics, indicated that they have not made use of the clause to address availability issues. In this case study we explore the application of Article 126a in Cyprus and Malta and examine alternative steps taken in Iceland to handle similar problems. The following section outlines the main availability problems encountered in these three countries.

8.1.2 Availability problems in Cyprus, Malta, and Iceland

Availability problems in Cyprus

Cyprus has a population of 862,011[56] and acceded to the EU in 2004. When Cyprus harmonised its legislation in 2001, it was given a five-year period to upgrade pharmaceutical dossiers in accordance with EU legislation[57]. Stakeholders consulted reported that whilst efforts were made to upgrade dossiers through various procedures, many marketing authorisation

[56] Eurostat figure. Available at: http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&init=1&plugin=1&language=en&pcode=tps00001

[57] The "upgrade of the dossiers" is the initiative taken by the EC to ensure that all the medicinal products in MS accessing the EU in 2004 would be in line with the requirements of EU legislation. According to the 2007 HMA report on availability of medicinal products and stakeholders interviewed for this study, in order not to go through the procedure of a full update of the dossier, some companies decided not to authorise the product in a new EU Member State, sometimes resulting in a reduced number of authorised products especially in the smaller MSs.

holders (MAHs) decided not to upgrade their dossier in the context of EU accession and left the Cypriot market. The consequence of this was that of the approximate 5,000 registrations Cyprus had before 2001, only approximately 500 medicinal products remained registered[58]. In terms of the potential impact of unavailability in public health, stakeholders in Cyprus noted that the products most likely to be missing from the market are products with ATC codes N (Nervous system), A (Alimentary tract and metabolism) and V (Various).

In addition, according to Cypriot stakeholders, between 2007 and 2009 Cyprus was involved as a concerned Member State in approximately five per cent of all Mutual Recognition Procedures, a percentage that stakeholders viewed to be low. This indicates that a position where there had been a very significant reduction in availability in the immediate post-succession period was not subsequently helped through the Mutual Recognition Procedures, and this despite the relatively low authorisation costs in Cyprus (circa €1,000) which had been set to encourage manufacturers to choose Cyprus as CMS in MRP.

In terms of centrally authorised products, there are 636 products approved with a centralised authorisation of which 271 applied for the price list in Cyprus. This suggests that even when products are authorised, many MAHs decide not to market their products in Cyprus.

Availability problems in Malta

Malta has a population of 416,110[59]. Before accession to the EU, Malta had limited regulation of medicinal products. For manufacturers, only a Certificate of Pharmaceutical Products (CPP) was required. The CPP was not considered by regulatory bodies to be sufficient to ensure the good quality, safety and efficacy of medicines available in Malta and it is acknowledged by authorities in Malta that the EU regulatory regime regarding authorisation of medicinal products has brought improvement in the quality, safety and efficacy of products[60]. However, as was the case in Cyprus, accession to the EU resulted in a reduction in the number of authorised medicinal products, causing availability issues in the country. According to the interviewed stakeholders, Malta went from having around 7,000 authorised products to having authorisations for less than half of these products by the end of the transition period in December 2006[61]. Maltese stakeholders also pointed to lack of availability of certain types of products, such as those related to parasitic diseases (although these are also rare in Malta).

As is the case with Cyprus and other smaller Member States, stakeholders have indicated that Malta is rarely included as a CMS in applications. In 2010, In order to increase the number of authorised products, Maltese national authority reached an agreement with national authorities in the United Kingdom and Ireland whereby a MAH that submits an application to these Member States is invited to include Malta as a CMS in authorisation procedures. This cooperation has

[58] These figures were provided in an interview with a stakeholder; however we have not been able to verify the information using external data.
[59] Eurostat figure. Available at: http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&init=1&plugin=1&language=en&pcode=tps00001
[60] Bugeja, V. (2008), 'The impact of EU legislation on medicines in Malta', *Journal of the Malta College of Pharmacy Practice*, 14
[61] The estimates vary according to sources and to different ways of counting the products. In Vella Bonanno, P. Seven years of EU pharmaceutical regulation in Malta. *WHO Drug Information* Vol. 25, No. 4, 2011, the figure goes down to only 2,410 products (excluding centrally authorised products). However, according to stakeholders interviewed for this project, the figure is even lower: 1,200 products.

had a positive impact and by 2011 an increase in the number of instances of Malta being used as a CMS was noticed. That year, Malta was included as a Concerned Member State in 51% of the average procedures[62].

Availability problems in Iceland

Iceland has a population of 319,575[63]. As it is the case in Cyprus and Malta, Iceland, another small and remote market, suffers from unavailability of medicinal products. The following table based on information available at the the Icelandic Medicines Agency (Lyfjastofnun) website[64] shows the situation in the country in terms of availability, showing that less than half of authorised products in Iceland are actually available on the market.

Table 5: Number of authorised products and products available in the market in Iceland

	Number of products authorised	Percentage
Marketed	2,227	49%
Not marketed	2,280	51%
TOTAL	4,507	100%

Source: Icelandic Medicines Agency (Lyfjastofnun) Database

Although the available data on the Icelandic Medicines Agency database has not allowed to determine what is the coverage in terms of ATC codes and therefore active substances, the analysis presented in Section 4.3 of the report shows that the number of ATC codes present in the Icelandic market is smaller than the number for other larger Member States. This means that a certain number of codes is not covered by authorised products, and therefore, for some active substances and indications there may be no products available. It is then possible that the needs of certain patient groups remain potentially unmet using the available products.

Iceland is not a EU Member State, but as a member of the European Economic Area (EEA) the country participates in the EU's Internal Market. EU pharmaceutical legislation is applicable in Iceland but the country has of course not experienced any issues related to accession to EU such as dossier upgrading.

8.1.3 The legal framework

The Cyprus clause was introduced through Directive 2004/27/EC of 31 March 2004, when it became clear that new measures were necessary to address obstacles to the efficient running of the single market. With Directive 2004/27/EC, the Commission established that, in order to increase availability of medicinal products, in particular within smaller markets, it should, in cases where an applicant does not apply for an authorisation for a medicinal product in the

[62] Vella Bonanno, P. Seven years of EU pharmaceutical regulation in Malta. *WHO Drug Information* Vol. 25, No. 4, 2011
[63] Eurostat figure. Available at: http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&init=1&plugin=1&language=en&pcode=tps00001
[64] Database available at: http://www.imca.is/Licences_for_Medicinal_Products/Medicinal_Product_Information_(SPC)/ (Accessed June 2012).

context of the mutual-recognition procedure, be possible for a Member State to authorise the placing on the market of the medicinal product for justified public health reasons. It needs to be noted that the Article applies only to products complying with the *acquis* and hence cannot be used for products that have been removed from national market after enlargement due to non-compliance with the acquis.

Further amendments to Article 126a were introduced by Directive 2010/84/EC to make it possible for Member States to allow the relevant stakeholders to deviate from certain provisions of Directive 2001/83/EC related to the requirements for labelling and packaging in order to address severe availability problems.

Article 126a of Directive 2001/83/EC

1. 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.

2. When a Member State avails itself of this possibility, it shall adopt the necessary measures in order to ensure that the requirements of this Directive are complied with, in particular those referred to in Titles V, VI, VIII, IX and XI. Member States may decide that Article 63(1) and (2) shall not apply to medicinal products authorised under paragraph 1.

3. Before granting such an authorisation a Member State:

(a) shall notify the marketing authorisation holder, in the Member State in which the medicinal product concerned is authorised, of the proposal to grant an authorisation under this Article in respect of the product concerned; and

(b) may request the competent authority in that Member State to submit copies of the assessment report referred to in Article 21(4) and of the marketing authorisation in force in respect of the medicinal product concerned. If so requested, the competent authority in that Member State shall supply, within 30 days of receipt of the request, a copy of the assessment report and the marketing authorisation in respect of the medicinal product concerned.

4. The Commission shall set up a publicly accessible register of medicinal products authorised under paragraph 1. Member States shall notify the Commission if any medicinal product is authorised, or ceases to be authorised, under paragraph 1, including the name or corporate name and permanent address of the authorisation holder. The Commission shall amend the register of medicinal products accordingly and make this register available on their website.

5. No later than 30 April 2008, the Commission shall present a report to the European Parliament and the Council concerning the application of this provision with a view to proposing any necessary amendments.

According to the article, when a Member State applies this provision, it should also adopt all the necessary measures to ensure that the requirements for the labelling and package leaflet, classification of the medicinal product, advertising, pharmacovigilance and supervision and sanctions are complied with. To make the Cyprus clause procedure more flexible, Directive 2010/84/EC introduced amendments to the second paragraph of Article 126a. These amendments mean that Member States may decide that Article 63(1) and (2) shall not apply to medicinal products authorised under Article 126a. Article 63(1) establishes that labelling of medicinal products shall appear in the official language or languages of the Member State where the product is placed on the market. Article 63(2) stipulates that the package leaflet must be clearly legible in the official language or languages of the Member State in which the medicinal product is placed on the market.

The specific mechanisms chosen by the Member States to put into practice this provision should be set out in the relevant national legislation implementing Directive 2004/27/EC[65]. This means that national authorities must determine the methods for exercising and controlling the responsibility vis-à-vis the placing in the market of the product in question and in relation to pharmacovigilance. Nonetheless, in a parliamentary response[66], the Commission made clear that using this mechanism for authorisation did not exonerate the MAH of any obligations emanating from EU legislation.

According to the Commission, the implementation of Article 126a should follow the same principles that already apply in the context of parallel import of products authorised nationally or parallel distribution of products authorised through the centralised procedure. The fact that a product is imported or parallel distributed does not exempt the holder of the authorisation of its obligations under the license. In addition, the parallel importer or distributor when they are involved in the distribution must comply with the obligations contained in the legislation, including Title VII of Directive 2001/83/EC.

Stakeholders have indicated that in the national legislation of many countries, procedures to authorise a product using Article 126a need to be initiated by a company and forms to apply for authorisation under Article 126a are available on the websites of the national competent authorities of Cyprus and Malta[67].

Member States should inform the Commission when they make use of the provision and the Commission publishes a publicly accessible register of the medicinal products concerned. The list is available online[68]. According to the list, the provision has been used in more than 600 instances by Cyprus, four times by Poland and once by Lithuania. The list however does not

[65] ENTR/F2/BL D(2002) VOLUME 2A Procedures for marketing authorisation CHAPTER 1 MARKETING AUTHORISATION November 2005 (Revision 3). http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap1_2005-11_en.pdf

[66] See http://www.europarl.europa.eu/sides/getAllAnswers.do?reference=E-2005-0026&language=FR

[67] Pharmaceutical Services, Ministry of Health, Cyprus: http://www.moh.gov.cy/moh/moh.nsf/page59_en/page59_en?OpenDocument; Malta's Medicines Authority: http://www.medicinesauthority.gov.mt/marketingauth.htm

[68] The list of medicinal products authorised under Article 126a is available at: http://ec.europa.eu/health/documents/community-register/html/except_index.htm

include medicinal products authorised via Article 126a in Malta even though according to the Maltese Medicines Authority's such list can be accessed on its website[69].

8.1.4 Application of the Cyprus Clause

This section focuses on the use of the Article in Cyprus and Malta and examines the situation in Iceland, another small and remote country, as well as more broadly within the EU.

Use of Article 126a in Cyprus

According to Cypriot stakeholders, Article 126a has allowed for additional products to be introduced in the national market. Now, there are around 4,000 registered medicinal products in Cyprus. Of these, about 3,200 are included in the price list, meaning that 800 are registered but not currently available. Of the 3,200, 2,500 are actually marketed. Of the around 4,000 product authorised, 530 have been authorised via Article 126a (the figure amounts to 611 according to the List of medicinal products authorised under Article 126a of Directive 2001/83/EC[70]).

From a stakeholder's perspective, other provisions, such as Article 5.1 (named patient), are a more effective way than Article 126a to bring products into the market when the products are needed quickly and for a small number of patients (5 to 10 patients). Stakeholders in Iceland also share this view. National authorities in Cyprus also consider the procedure under Article 126a to be lengthy when compared to the procedure related to Article 5.1 as it needs to be initiated by the product manufacturer and the packaging and labelling of the product need to be amended.

Use of Article 126a in Malta

The measures taken in Malta to improve availability of medicinal products and increase authorisations meant that the number of authorised medicinal products increased compared to the situation in December 2006. By the end of June 2011, 3,691 products were authorised, covering 1,339 active ingredients[71].

Following the update of Directive 2001/83/EC through Directive 2004/27/ EC in October 2005, Malta started using the provisions of article 126a in order to address their public health need and make products available in the country. The use of article 126a has proved to be beneficial to cover gaps in therapeutic availability, particularly for products that may not be economically attractive to manufacturers[72].

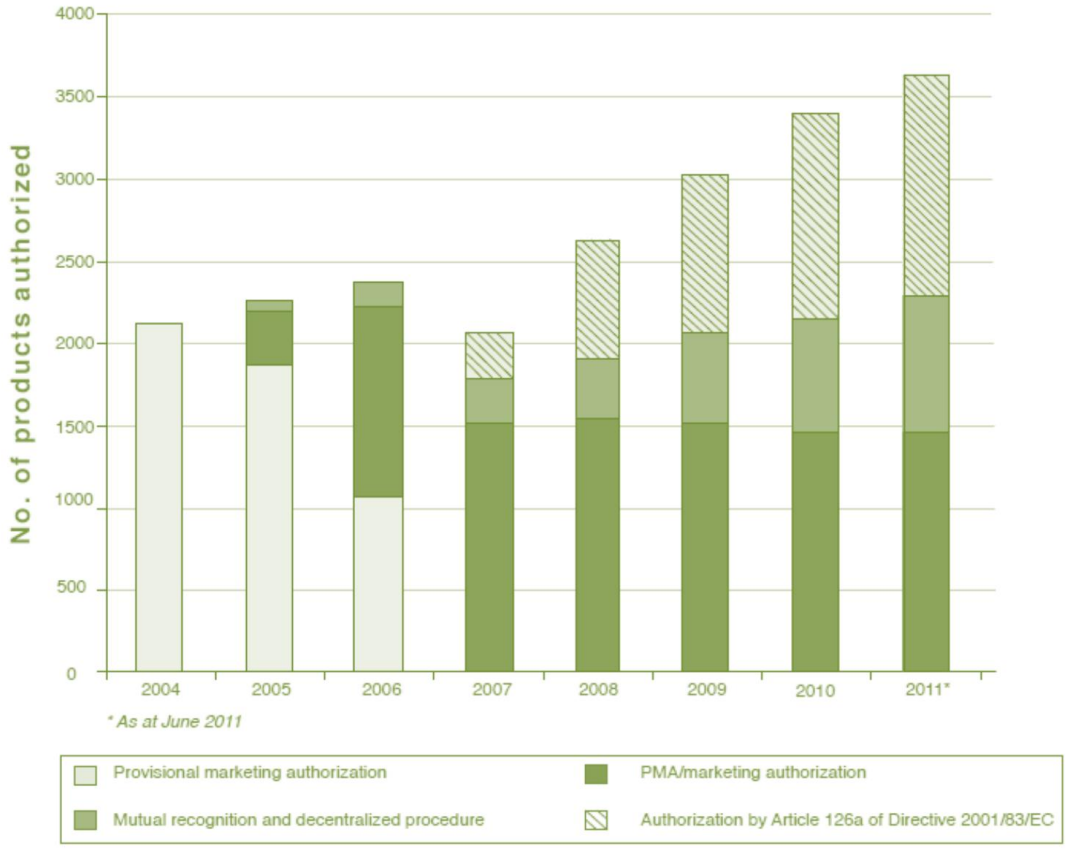
Around 1,500 products have been authorised through article 126a, covering gaps in therapeutic areas[73]. In addition, 636 products have been authorised by the European Commission through

[69] See http://www.medicinesauthority.gov.mt/marketingauth.htm
[70] See http://ec.europa.eu/health/documents/community-register/html/except_index.htm
[71] Vella Bonanno, P. (2011), 'Seven years of EU pharmaceutical regulation in Malta', *WHO Drug Information* Vol. 25, No. 4, 2011.
[72] Vella Bonanno, P. (2011), 'Seven years of EU pharmaceutical regulation in Malta' *WHO Drug Information* Vol. 25, No. 4, 2011.
[73] According to information provided in an interview with a stakeholder, 1,498 products have been authorised in line with regulation 4(2) of the Medicines (Marketing Authorisation) Regulations, in accordance with article 126(a) of Directive 2001/83/EC. The information is also available in Malta's Medicines List (http://www.medicinesauthority.gov.mt/marketingauth.htm)

the centralised procedure. There was an increase of 168% in the number of products available and of 72% in the number of active ingredients[74].

According to stakeholders, Article 126a is used as broadly as possible in Malta. If a certain product is not available, Malta allows it to be licensed and brought in using Article 126a, even if there is another product with same active ingredient available in the market. This, however, seems to suggest that products may be brought onto the market using Article 126a even in cases where a public health need for doing that is unclear.

Figure 19: Number of medicinal products authorised to be placed in the market by authorisation procedure in Malta'



Source: Vella Bonanno, P. Seven years of EU pharmaceutical regulation in Malta. WHO Drug Information Vol. 25, No. 4, 2011.

In the absence of a marketing authorisation for a medicinal product and in line with Article 126a, the Licensing Authority in Malta may authorise the placing of that medicinal product on the market, provided that the said product is authorised in another Member State (EU/EEA country). The authorisation is granted in accordance with Regulation 4(2) of the Medicines (Marketing Authorisation) Regulations, under the Medicines Act, 2003

[74] Vella Bonanno, P. (2011), 'Seven years of EU pharmaceutical regulation in Malta', *WHO Drug Information* Vol. 25, No. 4, 2011.

According to the information available on the website of the Maltese NCA[75], the authorisation procedure is being applied mainly to cover "the public health need created by the lack of applications for marketing authorisations for products which were on the derogation list[76] and for products which were authorised in the period between the publication of the derogation list and the date of accession". In the information made available online by Maltese national competent authorities, the procedure should in no way be considered as an easy way of circumventing the current procedures stipulated by the EU legislation or as a 'fast-track' procedure. They clarify that MRP and DCP have to be used for products that are being authorised in the EU/EEA and Malta should be included as a CMS in these procedures. Applications may not be considered for products for which the marketing authorisation is withdrawn by the MAH (other than for safety reasons) and subsequently received through the 'article 126(a)' route. Also, authorisations are not accepted if:

- they have been granted in accordance with article 126a for which a repeat use MRP has in the meantime (since date of authorisation) been carried out, and Malta was not included as Concerned Member State, will not be renewed; or
- they have been received in accordance with article 126a for products for which a MRP (first or second wave) or a DCP have been started from 1 August 2010 where Malta was not included as CMS.

In addition, Maltese authorities clarify in their website that from 1 August 2010, applications in accordance with article 126a which should be submitted as line extensions to products having a marketing authorisation may not be accepted and applicants will be directed to submit these applications as national line extensions.

Use of Article 126a in Iceland

In contrast to the situation in Malta and Cyprus, Article 126(a) has so far not been used in Iceland. The Icelandic Medicinal Agency understands that art. 126(a) should only be used when there are "justified public health reasons", and they interpret this in a narrow sense. According to stakeholders, Iceland has taken a different approach to deal with unavailability of medicinal products in the market and they proactively contact all companies to increase availability. They consider this approach to be effective.

When the Medicines Agency in Iceland identifies a product being authorised through centralised procedure, they contact the MAH to ask for the product to be marketed. Stakeholders interviewed for the study have explained that once the product is authorised in their country, it is not difficult to make it available as it is easy for companies to distribute in Iceland. The Medicines Agency takes also a proactive role helping companies making arrangements with wholesalers and in very short delays.

[75] See http://www.medicinesauthority.gov.mt/marketingauth.htm

[76] In Malta, products registered with a World Health Organisation (WHO) Certificate of Pharmaceutical Product (CPP) were included in a transition list which was drawn up in November 2002. The products were bound to benefit from a derogation. The derogation period in which products in the transition list could be registered via a Provisional Marketing Authorisation (PMA) followed by a Marketing Authorisation (MA), ended in December 2006. (In Bugeja, V. The impact of EU legislation on medicines in Malta. *Journal of the Malta College of Pharmacy Practice*. Issue 14 Summer 2008).

If DCP or MRP are used, national authorities ask the company to include Iceland as CMS. They try to work with RMS that have a very low or no fee to include Iceland in the procedure. They also respect the assessment of RMS and do not impose additional requirements to authorise products. This has enabled to simplify and decrease the costs of MAH to authorise products in Iceland According to stakeholders, after using such approach once, companies tend to include Iceland in subsequent procedure.

To stakeholders, one of the reasons for the difficulty in using article 126(a) is the national language. In Cyprus the national language is Greek, making it easier for Cyprus to place in the market medicinal products originally manufactured for Greece. In Malta, there are two official languages, Maltese and English, making it possible to place in the market medicinal products originally manufactured for the UK and Ireland. According to the Icelandic NCA, this means it is easier to apply article 126(a) in Cyprus and Malta than in Iceland.

National authorities in Iceland have also indicated that another reason why they do not rely on Article 126a to solve availability problems are safety issues linked to the use of the provision, as they may not know enough about the medicinal product in question.

Use of the Cyprus clause in other Member States

In our consultation about the awareness and use of the different provisions addressing availability in the EU legislation, stakeholders provided their views on the use of the Cyprus clause. In larger countries, although there is awareness of the provision and it has generally been transposed to national legislation, national authorities do not make use of Article 126a to deal with availability problems[77]. Several stakeholders consulted for the study have mentioned that Article 126a could benefit from further clarification in terms of who should take responsibility for the product. According to these stakeholders this provision leaves several interpretation issues up to Member States, exposing the Member State to the possibility of court cases due to interpretation. Some stakeholders have indicated that there may be safety problems related to the use of the Cyprus clause, since the national agencies may have little or no information about the product in question and, as mentioned before, it is not clear who is responsible for the product.

These issues were also noted in the 2007 HMA report[78], where a number of issues related to the application of the Cyprus clause were identified. These included for example the division of responsibilities if the MAH does not register a product in a specific Member State. According to the report, when applying Article 126a the Member States should make sure who would take responsibility with respect to translation of the product information and with respect to pharmacovigilance, as these responsibilities may fall on the MAH or the importer/special marketing authorisation holder.

This concern over the Article was also reflected in a European Parliamentary question on 18 January 2005[79]. In the response to this question concerning responsibilities[80], the Commission

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[78] Heads of Medicines Agencies (2007), 'Availability of Human Medicinal Products – Report of Task Force of HMA MG', http://www.hma.eu/.../Availability_medicines_HMAMG_TF_Report.pdf

[79] See http://www.europarl.europa.eu/sides/getDoc.do?type=WQ&reference=E-2005-0026&language=LV.

has indicated that it is incumbent upon Member States to determine the conditions of application of the provision, as it leaves to national authorities the choice of form and methods to achieve the result referred to in the first paragraph of the Article. Member States will need to determine the methods for the exercise and control of responsibility for the marketing of the products concerned and for pharmacovigilance.

According to the 2007 HMA report[81] manufacturers cite two broad arguments against the Cyprus clause. Firstly the reports cites the concern that bringing a product onto the market through the use of the Cyprus clause may put unintended responsibilities to the company. Secondly, the reports states that use of the Cyprus Clause may also draw attention of the EC or other MS to the fact that the company does not want to apply for MA in that particular country through MRP.

8.1.5 Conclusions

Examining the application of Article 126a in Malta and Cyprus, the interpretation of the provision in the respective national legislation appears to be relatively broad. Although restricted to products meeting specific requirements, these Member States seem to consider Article 126a as an additional procedure for authorising products nationally. The case law has established in 2011 that for articles 5(1) and 126a, the exemptions from the general rule to place a product in the market should be interpreted strictly. The Opinion[82] of the Court for the case C-185/10 (Commission Vs. Poland), states that:

> [22] Directive 2001/83 provides for the mutual recognition of marketing authorisations granted in other Member States thereby ensuring that marketing authorisation can be applied for in several Member States without subjecting the medicinal product to multiple authorisation procedures.
>
> [23] There are two exceptions to this general rule. A Member State may derogate from Article 6 provided that the special needs requirement is fulfilled (Article 5 of Directive 2001/83), or if it is necessary for public health reasons (Article 126a of Directive 2001/83). As exceptions, these provisions must be interpreted strictly.

It should be noted here that stakeholders in Malta and Cyprus, where Article 126a is widely used, expressed their opinion that the provision should be left intact, although they have also indicated that they do not consider the Cyprus clause to be an optimum tool and that they could eventually stop using this provision if, for example, the MRP would include all Member States. In contrast, authorities in other Member States understand how the use of Article 126a may be helpful for small Member States such as Malta and Cyprus to bring products into their markets,

[80] See http://www.europarl.europa.eu/sides/getAllAnswers.do?reference=E-2005-0026&language=LV
[81] Heads of Medicines Agencies (2007), 'Availability of Human Medicinal Products – Report of Task Force of HMA MG', http://www.hma.eu/.../Availability_medicines_HMAMG_TF_Report.pdf
[82] See http://curia.europa.eu/juris/document/document.jsf?text=&docid=110221&pageIndex=0&doclang=EN&mode=req&dir=&occ=first&part=1&cid=1002690

however they have also considered that the Cyprus clause is not an optimum solution as there may be safety issues regarding the medicinal products in question.

When discussing the Cyprus clause, the 2007 HMA report on availability of human medicinal products concluded that the value of this type of provision is “minimal and cosmetic”. This is not the view of all Member States, especially Malta and Cyprus. However, as the report also noted, many stakeholders consulted for this study agree that changes to the CP, the MRP and the DCP may be more effective in dealing with unavailability. These proposed changes have been discussed in detail in Section 6.0 of the report, but they include measures such as:

- introducing an Automatic/Simplified Mutual Recognition Procedure to work as a routine approach to authorise products in small markets;
- introducing an obligation to market the product across the EU when applying for Centralised Procedure; and
- introducing more flexibility around the Decentralised Procedure when including additional MS (e.g. small Member State) during the on-going DCP procedure.

Working towards making procedures more affordable where smaller MS are concerned (or MS experiencing shortages) has also been suggested as a measure that could help tackle unavailability of medicinal products more effectively.

Stakeholders have noted that, until there is effectively a single market for medicinal products in the EU, the problem will persist. In the meantime, Article 126a as helps to address some availability gaps. Until longer term solutions are agreed upon, it may be valuable to explore the possibility of amending the provision to align the legislation to the interpretation that smaller countries such Malta and Cyprus have done of the provision in practice. Another potential step forward could be to introduce amendments to the Article, to further clarify the responsibilities of MAHs, in order to facilitate the use of the clause by other Member States facing availability problems. The further strengthening of controls when the provision is used should also be considered. More broadly the Commission should further assess the potential for the approach adopted in Iceland to provide an alternative template to that offered by Article 126a.

8.2 Case study 2: Impact of shortages and supply problems and use of Article 81

Member states	EU27
Interviewees	Interviews with NCAs Published reports and news articles

8.2.1 Background

An important aspect of the broader issue of medicinal product availability relates to the availability of products that are authorised and marketed, but are still subject to availability challenges. The three main drivers of such availability are:

- supply shortages caused by unexpected changes in demand for products;
- disruptions in supply due to a variety of factors affecting the global supply chain; and
- supply shortages resulting from decisions of actors in the medicinal supply chain.

Such availability problems have been noted by a large number of National Competent Authorities consulted as part of the study, and, given that these availability problems may affect essential medicines or medicines without substitutes, they may have substantial public health impact. This case study explores the specific problems and their drivers in more detail and investigates the role of EU legislative provisions in addressing these availability problems.

Medicinal supply chain

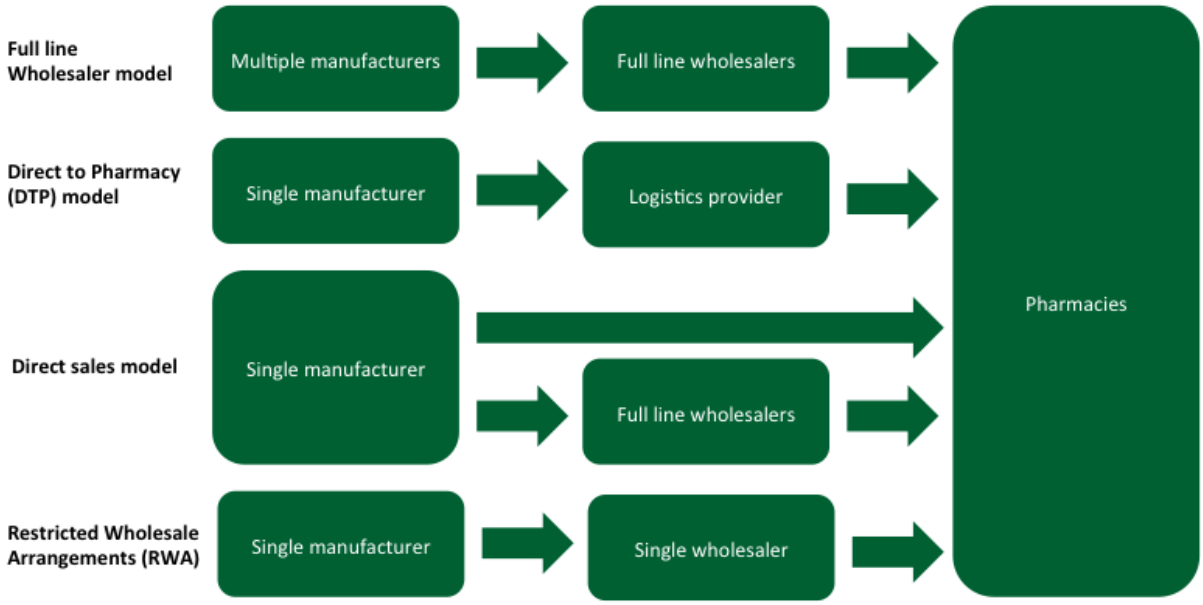
The supply chain for medicinal products is a complex one. It includes three main actors:

- **Manufacturers** – manufacturers are authorisation license holders who produce the products in question, often using sites located across the globe;
- **Wholesalers/distributors** – wholesalers are authorised to supply medicinal products to pharmacies and health professionals; and
- **Pharmacies, hospitals, and dispensing doctors** – pharmacies are bodies responsible for supplying products to the public, while hospitals and dispensing doctors supply the products directly to their patients

It is also important to note that there are different models of supplying products to pharmacies. Although full-line pharmaceutical wholesalers (wholesalers carrying the full-line of medicinal products from all manufacturers) are responsible for a large proportion of the medicinal product supply in the six largest EU markets (France, Germany, Italy, Netherlands, Spain, and the United Kingdom), other distribution methods, such as Direct to Pharmacy (DTP), direct sales, and Reduced wholesale Arrangement (RWA) are gaining in popularity[83]. These are outlined in the figure below.

[83] IPF (2012), 'Distribution Profile and Efficiency of the European Pharmaceutical Wholesale Industry', http://www.ipf-ac.at/uploads/media/GIRP_IPF_clean_FV_120112.pdf

Figure 20: Distribution models



Source: IPF (2012), 'Distribution Profile and Efficiency of the European Pharmaceutical Wholesale Industry', http://www.ipf-ac.at/uploads/media/GIRP_IPF_clean_FV_120112.pdf

The different arrangements are of importance, since they mean that the stakeholders involved in the supply chain will vary and so will their roles. For instance, although full-line wholesalers act as logistic providers under the DTP model, they do not own the products, while in the case of direct sales model, there are instances where no distributors or wholesalers are involved in the supply chain[84]. As a result, any provision aiming to secure the consistent supply of medicinal products by targeting the actors in the supply chain needs to take in account the different emerging models.

8.2.2 Availability problems and problem drivers

The following sections outline the three main types of shortages and their drivers.

1. Shortages due to short notice changes in demand for products

The first type of shortage is linked to public health developments leading to demand quickly outstripping supply. One example is that of Norway, where, according to one stakeholder, shortages of antibiotics in 2011 and 2012 resulted from an unexpected increase in the cases of mycoplasma pneumonia. However, such problems have not been identified in other Member States and it therefore appears that most shortages stem from problems occurring on the supply side.

2. Disruptions in supply

[84] IPF (2012), 'Distribution Profile and Efficiency of the European Pharmaceutical Wholesale Industry', http://www.ipf-ac.at/uploads/media/GIRP_IPF_clean_FV_120112.pdf

One of the supply-side availability problems relates to problems and disruptions that take place at the manufacturing stage. Stakeholders from Belgium and Ireland identified availability problems in their respective Member States related to manufacturing sites being temporarily shut down and the time needed to restart production. Specific examples of products recently affected by such problems include:

- **Simponi pre-filled pens** – Simponi is an anti-inflammatory product. In February 2011 a manufacturing defect in some batches of pre-filled pens was discovered at a manufacturing site of Janssen Biologics B. V. the company producing Simponi. This resulted in a halt of production, which expected to result in supply issues over following three months[85].
- **Caelyx** – Caelyx is an anti-cancer product used to treat metastatic breast cancer, advanced cancer of the ovary, Kaposi's sarcoma, and multiple myeloma. In Autumn of 2011 the manufacturer, Janssen-Cilag, started facing capacity problems at the Ben Venue Laboratories in the US, which, together with an ongoing investigation concerning the manufacturing process resulted in a delayed release of batches of Caelyx for the EU market[8687]
- **Vfend** – Vfend is an antifungal medicine used to treat fungal infections. In January and February of 2012, Pfizer Limited, the producer of Vfend, noted manufacturing problems at two sites producing Vfend, which resulted in shortages expected to last several weeks.
- **Cytotoxic products** in Poland – Problems at the Sandoz manufacturing site in Austria were seen as the source of shortages of a range of cytotoxic anti-cancer products (in particular etoposide, cisplatin, fluorouracil, doxorubicin, epirubicin, gemcitabine) in Poland and neighbouring Member States in 2012[88]

Some of the availability problems can also result from the fact that active ingredients can require particularly complex **logistical arrangements**. One example is that of protamine-containing medicines. Protamine sulphate is used to counteract the anticoagulant action of heparin, as well as to neutralise the effect of heparin. It is a "purified mixture of simple proteins obtained from the sperm or roe of wild salmon"[89]. This species of salmon has traditionally been fished on the north-eastern part of the coast of Honshu Island in Japan. Activity in this area stopped following the 2011 earthquake and tsunami in Japan, leading to a potential shortage of protamine. The problem was solved when protamine sulphate sourced from the fishing grounds in Hokkaido in Japan was deemed to be equivalent. Nevertheless, the example illustrates potential availability problems for products with a complex supply chain, especially where active substances are only available from a specific site.

[85] EMA (2011), 'EMA/126688/2011 - Questions and answers on the supply shortage of Simponi pre-filled pens'
[86] EMA (2011), 'EMA/718827/2011 - Shortage of Caelyx (doxorubicin hydrochloride)'
[87] EMA (2012), 'EMA/152112/2012 - Questions and answers on the supply shortage of Vfend (voriconazole)'
[88] The Pharma Letter (2012), 'Cancer Drug Shortages persist in Poland', 26 April 2012' http://www.thepharmaletter.com/file/112884/cancer=-drugs-shortages-persist-in-poland.html
[89] EMA (2012), 'EMA/CHMP/717405/2012 - Press release - European Medicines Agency completes review of protamine-containing medicines'

In some instances of shortages, one of the factors leading to closure of sites and stoppages are quality inspections. These inspections focus on compliance with Good Manufacturing Practice (GMP). GMP relates to a set of principles and guidelines that apply to the manufacturing of medicinal products. These principles are mandatory for all manufacturing authorisation holders (manufacturers and importers) in the EU and are enforced through inspections[90]. Shortages of medicines observed in the recent years in the EU (such as those in the examples above) highlighted the link between GMP compliance and shortages, given that instances of non-compliance can result in the need to halt production. An EMA report from October of 2011 recognised the key problems associated with balancing GMP requirements and the need to ensure availability of essential products. The three elements of the "regulator's dilemma" are as follows:

- in some cases defective medicines need to be left on the market, since the risk of shortages is greater than the risk of exposure to the defective products;
- regulators cannot always take action against a manufacturing site due to availability implications; and
- there are external factors which make switching patients over to alternative medicines difficult which further restrict the regulators'' ability enforce GMP rules[91].

The interaction between GMP requirements and availability is therefore an important issue. One of the interviewed stakeholders also noted that rising quality standards could mean that it becomes more difficult for producers to quickly restart aborted production lines. According to this stakeholder, particularly vulnerable products include more expensive products manufactured in smaller quantities or products that cannot easily be stored (i.e. insulin products).

Current recommendations with regard to the impact of GMP compliance on availability focus in particular on improved cooperation and risk-assessment. Nevertheless, there may also be scope for the revision of relevant GMP principles and guidelines to facilitate the work of regulators in instances where enforcing compliance can have an impact on availability. These implications will be discussed in the next sections.

3. Supply limitations resulting from decisions of actors in the medicinal supply chain

The final type of shortage is a shortage resulting from actions by actors in the supply chain. These actions are not intended to generate shortages, but in some cases they could lead to shortages with potential public health implications. One example is the reported halt to the shipment of medicinal products to Greece by the manufacturer Roche to Greek public hospitals due to unpaid invoices[92].

[90] See http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000154.jsp&mid=WC0b01ac0580027088
[91] EMA (2012), 'Reflection Paper on Product Supply: Lessons Learned and Proposed Recommendations'
[92] Phillips, L. (2011), 'Austerity cuts not to blame for Greek drug shortage, EU says', *EU Observer*, 19September 2011, http://euobserver.com/851/113667

Another availability problem in this category noted by full-line wholesalers and also some of the NCAs relates to quotas imposed on wholesalers and pharmacies by the producers. If a quota is exhausted, the producer will not supply the product to the wholesaler or pharmacist. According to stakeholders representing European full line wholesalers, the nature and the way in which quotas are communicated differ, but the main reasons behind quotas relate to manufacturers aiming to limit the parallel export of their products.

The UK is an example of a Member State where manufacturer quotas have resulted in supply issues, although the NCA noted that these restrictions are temporary and usually do not result in UK-wide supply problems. The UK NCA attributes the quotas to the manufacturers' attempt to restrict parallel trade, however there is no agreement that this is indeed the main source of the availability problems. The 2012 report of the all-party Pharmacy Group in the UK Parliament found the availability problems to be a direct result of parallel export by smaller wholesalers, rather than a result of manufacturers' response to parallel export[93].

According to EU full-line wholesalers, in addition to the problems in the UK (which now uses a predominantly Direct to Pharmacy model), such problems have also been noted in Austria, Belgium, and Italy. A particular problem according to the wholesalers is the fact that such quotas in some cases may not be communicated to the wholesaler, affecting their ability to effectively plan the supply of the product.

Overall, the products where the three types of shortages outlined above are likely to lead to the most severe availability problems include:

- Products where there is no effective substitute. A Lithuanian stakeholder noted that this is the case with heparin, some anticancer medicines, such as fluorouracil, tamoxifen and some antibiotics (e.g. oxacillin, ampicillin with sulbactam); and
- products relying on a single manufacturing site or a small number of manufacturing sites An Austrian stakeholder noted that an increasing dependency on a limited number of manufacturing sites, especially outside the EU, can mean that a potentially minor unexpected disruption can have substantial impact on availability.

The following section discusses the available provisions, which aim to address these availability problems.

8.2.3 EU Legal framework

The key legal provision relevant to ensuring that shortages of medicinal products are avoided is the Article 81 of Directive 2001/83/EU on the Community Code Relating to Medicinal Products for Human Use. The Article 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

[93] Furness, H. (2012), 'Drug Shortage Caused by Sales to EU, MPs say', *The Telegraph*, 15 May 2012 http://www.telegraph.co.uk/health/healthnews/9266416/Drug-shortage-caused-by-sales-to-EU-MPs-say.html

> 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[94].

This provision is transposed and implemented in practice through the public service obligations imposed on supply chain actors in individual Member States. According to consulted stakeholders, these differ between individual Member States in terms of the nature of the obligation, as well as to which actors the obligations apply to. Generally the public service obligations relate to the obligation on wholesalers and distributor to supply the domestic market. In many cases they do not apply to manufacturers supplying the distributors. This is of particular relevance in instances where manufacturer quotas may result in availability problems: Although the text of the Article does name marketing authorisation holders, according to wholesalers, obligations relating to manufacturers may not necessarily be transposed at a national level. In addition, the changing distribution models, outlined below, may mean that obligations for wholesalers may become less effective in ensuring supply.

Another important aspect relating to the Article 81 is the way the provision interacts with other elements of EU legislation. Article 81 states that:

> 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 movement of goods and competition[95].

One of the interviewed stakeholders however noted that the text of the article does not provide sufficient guidance as to the extent to which one can ensure that wholesalers supply the domestic market while at the same time not jeopardising the internal market. Public service obligations often set out that the wholesaler should first supply the domestic market, however there is not necessarily sufficient clarity as to what stocks should be held in reserve, nor is there necessary full compliance with this requirement. A Belgian stakeholder noted that this was the case in Belgium, resulting in availability problems on the domestic market.

Another area where the interaction between the principles in Article 81 and other provisions is important to consider is Good Manufacturing Practice. Article 117 of Directive 2001/83/EC sets out that the supply of a product can be prohibited if the product is harmful, lacks efficacy, its risk-benefit balance is not favourable, its ingredients are not as declared, and also if:

> the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled[96].

[94] Art 81 of Directive 2001/83/EC
[95] Art 81 of Directive 2001/83/EC
[96] Art 117 of Directive 2001/83/EC

It is important to note that no explicit mention is made of availability in the articles relating to prohibiting supply. In cases where a product is clearly harmful, the decision to halt production is a simple one, but in instances outlined above where the availability problems are likely to be more severe than potential problems with the given product, the above provisions provide limited guidance as to balancing concerns relating to GMP non-compliance and availability. Although the two provisions concern different actors (regulators and manufacturers/distributors), there is effectively no clarity as to conditions under which the obligation to ensure supply should takes precedent over GMP-compliance, if at all. One step in a direction of addressing this issue is Article 1(6) of Directive 2011/62/EU, which allows for exemption from some GMP (good manufacturing practice) requirements to aid availability, but it is yet to be seen how this provision works in practice.

8.2.4 Conclusions

Availability problems concerning products authorised and marketed appear to be common and can have significant public health implications, especially in the case of products with no substitutes. Complex global supply chains and reliance on fewer manufacturing sites makes products vulnerable to manufacturing and distribution disruptions, which can in turn result in availability problems. In addition enforcement of GMP compliance, as well producers' and wholesalers' actions with regard to parallel trade can occasionally further contribute to availability problems.

Although the problem derivers leading to shortages and supply disruptions are not linked to the authorisation process as such, it is still an area with a European dimension and where EU action would be valuable. At the moment, Article 81 is the key EU provision aiming to address such problems. However, given continued disruptions and shortages and the changing supply chain, there may be room for improvement. There are indications that the transposition and implementation of Article 81 remain fragmented. In addition, there appears to be scope for clarifying the interaction between the obligation to supply set out in Article 81 and other EU provisions concerning GMP compliance and parallel trade could constitute a step towards addressing the broader issue of medicinal product availability.

8.3 Case study 3: Common Baltic Package

Member states	Estonia, Latvia and Lithuania
Interviewees	NCAs: (primarily MT, LV, EE) National information and guidance documents

8.3.1 Background

The three Baltic countries, Estonia, Lithuania and Latvia, face similar problems in terms of availability of medicinal products. In the three Member States medicinal products are sometimes not authorised or authorised, but not marketed. National authorities in Baltic countries generally link availability problems to the size of their markets, which are relatively small and therefore more prone to unavailability, and to the fact that they are relatively new Member States within the EU. According to stakeholders consulted, the limited market sizes may mean that the Baltic markets cannot sustain profitability or that they have a limited reimbursement system. For example, according to the stakeholder consultation, in Latvia there are 4,644 medicines authorised, but only 67% of them are available in the market. In addition, only 10% from all centrally authorised medicinal products are available in Latvia.

In an attempt to alleviate availability problems and, at the same time "to save resources of stakeholders, to make approval of the common Baltic packages easier, smoother, quicker and more transparent"[97], the three Baltic States have agreed on a Common Baltic Package (CBP) procedure that simplifies the labelling of medicinal products in the national language. The CBP procedure entails a simplification of the procedures to assess and approve multilingual labelling and packaging for products authorised and marketed in at least two of the three Baltic States. The procedure is applicable to changes of the labelling requisites referred to in Article 61(3) of Directive 2001/83/EC as amended[98].

In this case study, we explore the development and application of the CBP as an example of how Member States are taking forward provisions present in EU legislation and build their own procedure around it. Introducing simplification in labelling procedures has been noted by stakeholders within the European Medicines Agency (EMA) as a good method for facilitating availability and is in line with current work around Articles 63(1) and 63(3) of Directive 2001/83/EC as amended that allow for labelling exceptions to, among other things, facilitate availability of medicinal products.

The CBP is a voluntary procedure for medicinal products exclusively authorised via National Procedure. The first recommendation for the Common Baltic Package was completed and signed in May 2005 and the procedure was updated in August 2009, when NCA Directors from Estonia, Latvia and Lithuania, signed a common package guideline setting out common

[97] See http://www.sam.ee/en/common-baltic-package-procedure

[98] Article 61(3) of Directive 2001/83/EC establishes that: "All proposed changes to an aspect of the labelling or the package leaflet covered by this Title and not connected with the summary of product characteristics shall be submitted to the authorities competent for authorising marketing. If the competent authorities have not opposed a proposed change within 90 days following the introduction of the request, the applicant may put the change into effect". The text of the 2001 Directive is available at: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83/2001_83_ec_en.pdf

principles for labelling. The current Common Baltic Package procedure introducing the concept of a single assessment of applications was agreed in February 2011.

According to the stakeholder consultation, the procedure applies to medicinal products authorised via National Procedure before 1 May 2004. In addition, the common Baltic package procedure applies only if the (invented) name of the medicinal product is the same in all Member States involved.

As the literature on the Common Baltic Package procedure is very limited, this case study is based on the input from the consulted NCAs in Estonia, Latvia and Lithuania.

8.3.2 The CBP procedure

The CBP procedure is a common procedure to approve the packaging for a product in all three countries by using one of them as the Reference Baltic State (RBS). The RBS is chosen using a rotation principle. In order to use a common Baltic labelling, Marketing Authorisation holders (MAHs) do not need to discuss the procedure with each medicinal agency separately. Instead, MAHs communicate only with the agency that is acting on behalf of all three Member states.

The prerequisites to apply for approval through the CBP procedure are as follows:

- the summary of product characteristics does not contain any differences that preclude harmonisation of the labelling;
- the name of the medicinal product is the same in all Baltic States;
- there is no ongoing variation procedure that could affect labelling; and
- there is no ongoing renewal procedure.

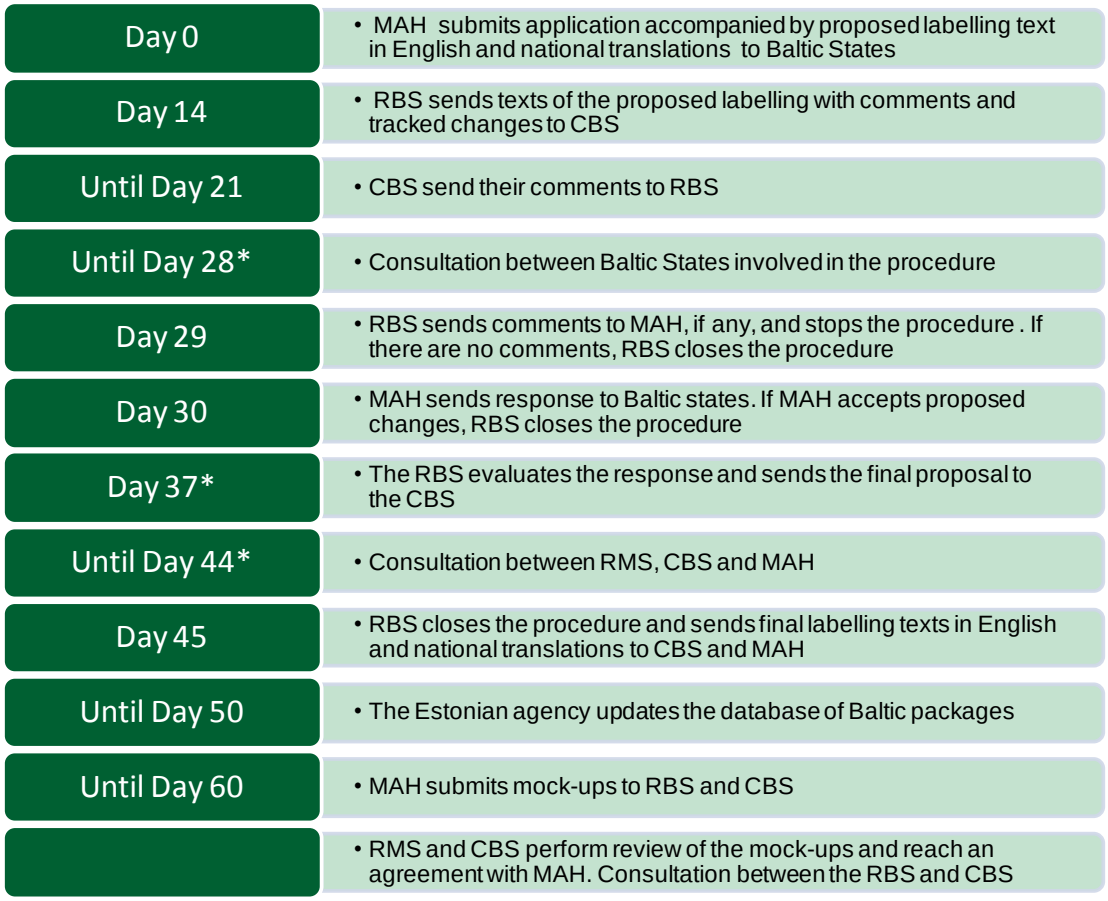
The requirements of Directive 2001/83/EC, Commission Guidelines on the readability of the label and package, as well as Common Baltic Guidelines shall apply in the procedure. In addition, the labelling shall comply with all relevant EU/EMA/QRD guidance documents, especially QRD (Quality Review of Documents) templates with explanatory notes.

To start the procedure, the MAH needs to submit an identical application for the Common Baltic Package procedure accompanied by the labelling text and national translations in Microsoft Word format to all participating Member States. The application and labelling text are submitted electronically and hard copies are not required. Once the application is submitted, the Baltic States agree on the RBS. The RBS then informs all Concerned Baltic State(s) (CBS)[99] and the MAH about the start of the procedure, performs an assessment of the English text and sends the proposal on the labelling to the CBSs within 14 calendar days. The CBSs shall send comments or agreement on the labelling text to the RBS and to each other within 7 calendar days. If the opinions of the national agencies differ, they should use their best endeavours to reach an agreement.

[99] The CBP procedure may concern only two of the three Baltic States.

The RBS shall send the agreed proposal on changes to the MAH, which has up to 14 calendar days to respond (for administrative purposes the clock is stopped until receiving the response). Once the response is received, the RBS has up to 7 calendar days to evaluate the MAH opinion and send a final proposal to the CBS. The CBS can send additional comments within 7 calendar days. In case of agreement, the RBS closes the procedure and sends the final labelling text to the MAH and CBS. After that, the MAH has up to 15 calendar days to submit mock-ups to RMS and CMS. The Estonian State Agency of Medicines is responsible for updating the database on Common Baltic Packages. The database is for internal use only and contains the names of the medicinal products and the dates the procedures have been finalised. The figure below provides an overview of the CBP procedure.

Figure 21: Overview of the Common Baltic Package procedure



* If needed
Source: The Common Baltic Package Procedure (available at: http://www.vza.gov.lv/doc_upl/common%20Baltic%20package%20procedure.pdf)

8.3.3 Impact of the CBP procedure

Since the establishment of the CBP, Latvia's State Agency of Medicines has received 20 applications. Of these, 13 CBP procedures have been approved, four procedures are in process, two procedures are in clock-stop (reference Baltic state is waiting answer from the applicant) and one procedure was rejected.

According to the medicines agencies in the three countries, it is generally not difficult for the Baltic authorities to reach an agreement. In one case, agreement was not reached because the indications for the product were different and therefore the application did not meet all requirements. All other procedures were positive.

With regard to the impact on availability, given that the number of the finalised procedures is still small, the relevant agencies were not in a position to draw major conclusions about the CBP. According to the stakeholder consultation, the reaction from the industry, especially of one vaccine manufacturer, was very positive and, according to the feedback received by one the Baltic NCAs, the single assessment is viewed as being easier for the MA holders.

There is no available data concerning cost-savings due to the CBP, but from the point of view of the MAH, the procedure is likely to bring about savings, since only one procedure is required when normally the labelling would have to be approved three times.

Baltic NCAs believe that the reason why the CBP is working well is the fact that the Baltic States share many features and are perceived by MAHs as one market. It is not clear however if other Member States would be able to join the procedure. Two of the three NCAs do not envisage this to happen, while the third one has noted that there is a discussion of the possibility of another Member State joining the procedure.

8.3.4 The CPB procedure and EU Legal framework

In August 2009, the Common Baltic Package Guidance[100] was updated to be in line with the amended Directive 2001/83/EC and the QRD template. Although according to stakeholders there was no communication with the EU and the Baltic NCA at the time the CBP was being developed, national authorities noted that the CBP procedure is consistent with the requirements for labelling described in the 2001 Directive as they were already implemented in national legislation.

According to the CBP guidance, applications for the Common Baltic Package Procedure must meet these requirements:

- The Common Baltic Package procedure is applicable to changes of the labelling requisites referred to in Article 61(3) of Directive 2001/83/EC as amended.
- The Common Baltic Package is acceptable only if the (invented) name of the medicinal product as referred in Article 1(20) of Directive 2001/83/EC as amended is the same in all states involved
- For the Common Baltic Package, requirements of Directive 2001/83/EC as amended and Commission Guideline on readability of the label and package leaflet of medicinal products for human use apply.

[100] See http://www.vvkt.lt/index.php?1305993728

- Labelling and package leaflet shall comply with relevant EU/EMA/QRD published guidance documents, especially QRD templates with explanatory notes.

As mentioned above, in this case study we are trying to explore how Member States interpret EU legislation and develop procedures around particular provisions in this case, Articles 61(3) and 63(1) of Directive 2001/83/EC. The provisions introduced by Article 63(1) are relevant in the context of the CBP as it allows for the use of multilingual packages, provided that the same particulars appear in all the languages used.

The CBP initiative seems to be aligned to the on-going work around labelling carried out within the EMA in relation to Articles 63(1) and 63(3) as a means to help improving availability of medicinal products, especially in small markets. Articles 63(1) and 63(3) of Directive 2001/83/EC as amended allow for labelling exceptions to, among other things, facilitate availability of medicinal products. Stakeholders at EMA have noted that simplification in labelling procedures seems to be as a good method for facilitating availability. There is currently a task force working on the issue of labelling in which countries with known availability problems such as Baltic States, Cyprus, Iceland, Malta are participants. In addition, stakeholders at the EMA have noted that the agency supports changes in labelling that mean including additional languages or new combination of languages in multilingual packages if these changes help alleviating shortages of medicinal products in some markets, especially in smaller ones.

Stakeholders within the pharmaceutical industry have indicated that initiatives such as the Common Baltic Package procedure could be further developed and be used as a platform to reinforce the mutual recognition of the MA decision by other countries, in particular for product access “regional” markets. As an example, stakeholders suggested that if a medicinal product has received marketing authorisation in one of the three Baltic countries it could automatically be recognised by other Baltic countries without significant additional fees as long as they apply for a common Baltic packaging. Such suggestion will need to be compliant with EU legislation, which is not the case at the moment. However, it may be worthwhile exploring the possibility of MAH applying for MRP, Repeat MRP and DCP choosing one or several groups of CMS, pre-selected on language/geographical basis, with only one national agency acting as the regional RMS within the group.

8.3.5 Conclusions

Although the applicability of the Common Baltic Package procedure is somewhat narrow (it only applies to products authorised nationally prior to 2004) the experience of national competent authorities in Latvia, Estonia and Lithuania is a positive one, since the procedure is seen as helpful in tackling availability problems. The CBP entails a single assessment of applications to proposed changes to an aspect of the labelling or the package leaflet and facilitates the use multilingual packages (as per Articles 61(3) and 63(1) of Directive 2001/83/EC) intended for the Baltic market. It would be worthwhile to further explore what features of the CBP can be applicable more broadly, especially in groups of countries sharing characteristics comparable to those of the Baltic States. One could imagine that more Member States could adopt multilingual packages or a single assessment procedure related to proposed changes to package labelling

or package leaflets. This could even be extended to applications for Marketing Authorisation concerning pre-defined groups of MS while using existing procedures such as MRP, Repeat MRP or DCP.

8.3.6 Case Study Appendix: Application form for the Common Baltic Package Procedure

APPLICATION FORM FOR THE COMMON BALTIC PACKAGE PROCEDURE

1. Baltic States

Participating Baltic States *	**Reference Baltic State ****
☐EE ☐LT ☐LV	☐EE ☐LT ☐LV

*Chosen by MAH.

** Agreed by Baltic States.

2. Medicinal product(s) concerned by this application *

	Estonia	**Lithuania**	**Latvia**
(Invented) name			
Strength(s) *			
Pharmaceutical form			
MA number(-s)			
Active substance(s)			
MAH			
name			
address			
Contact person			
name			
address			
e-mail			
phone			
Therapeutic indications **			
Posology and method of administration ***			

* All strengths may be included if proposed labelling text is the same.

** For non-presription medicinal only: please provide English translations of section 4.1 of SPS approved by RBS and CBS(s).

*** For non-presription medicinal only: please provide English translations of section 4.2 of SPS approved by RBS and CBS(s).

3. Declaration of the applicant

I hereby submit an application for the common Baltic package in accordance with the proposals given above. I declare that (*please tick the appropriate declarations*):

☐ There are no other changes than those identified in this application.
☐ National fees have been paid (if applicable).
☐ This application has been submitted simultaneously to all participating Baltic States.
☐ There is no other ongoing variation procedure that could affect the labelling.
☐ The renewal procedure is not ongoing.

4. Signature

Signatory_____ Job title
___ _____

Name Date
_____ _____
___ _____

8.4 Case study 4: Availability of anticancer medicinal products

Member states	EU27
Data sources	NCA Stakeholders Published reports

8.4.1 Background

Cancer medicines are a particularly important category of medicinal products. There are a number of reasons for this:

- Stakeholder consultation established cancer products to be one of the areas where availability problems are most acute.
- While mortality rate is falling, European incidence of cancer is increasing, suggesting that more people in the EU are receiving cancer treatment.
- Cancer products represent a substantial proportion of the pharmaceutical market (between 1987 and 2004, 8.1% of all unique pharmaceutical products introduced on the European market were cancer products[101])
- A large share of industry investment and innovation focuses on cancer products. As of 2005, approx. 15% of industry research expenditure focused on cancer products and 27% of all projects had a cancer-focused component[102]. In the context of the broader availability problems identified by stakeholder this would suggest that availability problems associated with cancer products could see patients unable to gain access to new therapies and treatments.

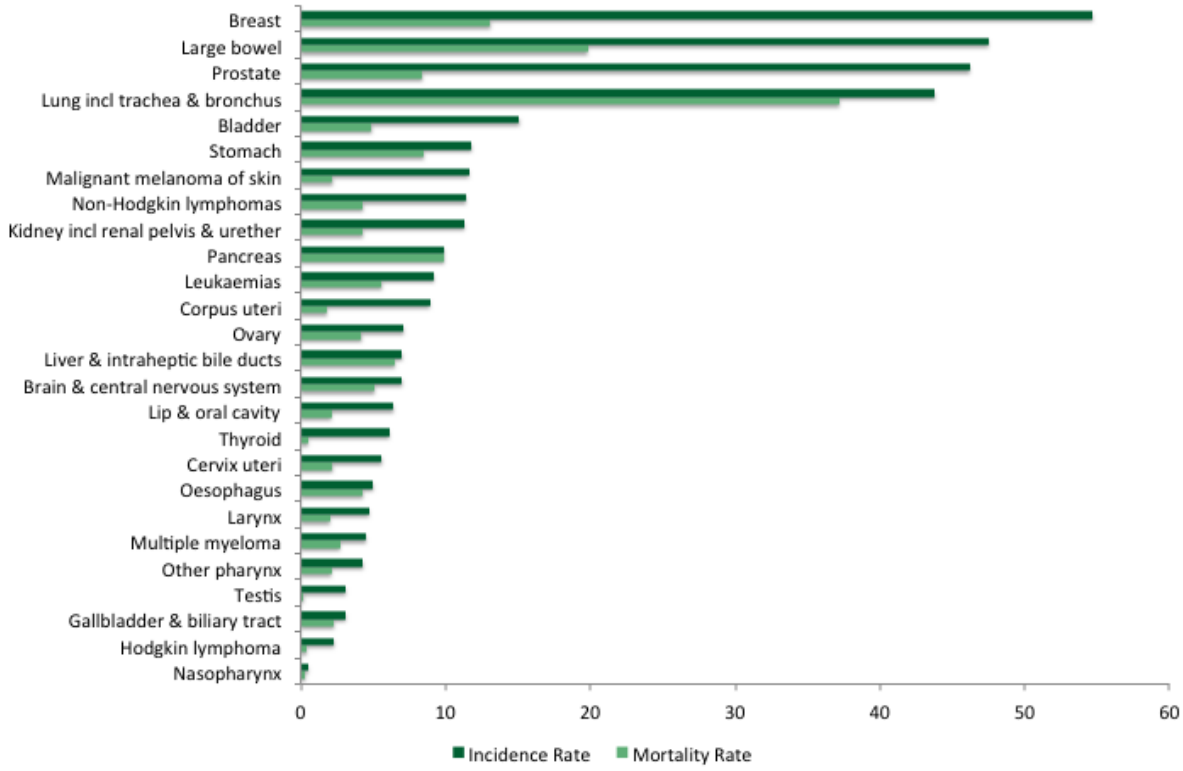
The following sections investigate availability problems associated with cancer medicines in more detail. It is important to note that cancer is a highly diverse area, where the nature and severity of conditions differs significantly, and so do the medicinal products designed to treat them. The next section sets out some of these differences. The following sections outline the availability problems associated with cancer products, the problem drivers, and outline the relevant EU provisions, focusing in particular on their role in ensuring availability of cancer products.

8.4.2 Incidence and mortality trends

The following figure based on 2008 EUCAN data outlines the incidence and mortality rates[103] for both sexes of different forms of cancer.

[101] Wilking N. and Jönsson, B. (2005), 'A pan-European comparison regarding patient access to cancer drugs', archive.eahp.eu/content/download/25383/.../SpecialReport76-77.pdf
[102] Wilking N. and Jönsson, B. (2005), 'A pan-European comparison regarding patient access to cancer drugs',
[103] Expressed per100,000 residents and age-adjusted to the standard European population

Figure 22: Incidence and mortality



Source: EUCAN Country Factsheets 2008

As one can see, there is substantial variation between different types of cancer. While some common cancers, such as breast or prostate cancer, have relatively low mortality, other more rare conditions (I.e. stomach or pancreas cancer) have mortality rates exceeding that of prostate cancer in absolute terms. This implies that in general terms any policy concerning cancer products needs to ensure effective treatment of common conditions, as well as rarer, but in relative terms more severe ones.

With regard to trends over time the overall incidence of cancer in the EU is increasing. The cancer incidence rate increased by 10% between 2004 and 2006, with the increase being attributed to factors such as aging population, increase in the number of female smokers, change in sun-tanning habits, and falling rates of reproduction. At the same time, the mortality rate has plateaued or decreased across Member States[104].

The final difference lies in variations between individual Member States. As the 2009 study patient access to cancer medicines in Europe notes, Hungary's incidence rate in 2006 was almost twice that of Bulgaria and in Nordic countries (i.e. Denmark and Sweden) the difference in incidence between men and women was lower than that in remaining EU Member States[105].

[104] Wilking N. and Jönsson, B. (2005), 'A pan-European comparison regarding patient access to cancer drugs', archive.eahp.eu/content/download/25383/.../SpecialReport76-77.pdf
[105] Wilking N. and Jönsson, B. (2005), 'A pan-European comparison regarding patient access to cancer drugs', archive.eahp.eu/content/download/25383/.../SpecialReport76-77.pdf

These differences can be attributed to the differences in some of the factors outlined above (i.e. prevalence of smoking), but also to the existence and effectiveness of screening programmes, where Member States with effective screening programmes are more likely to detect cancers and, as a result, report higher incidence rates.

In addition to differences in incidence rates, there is also a variation in mortality rates, which can be more closely linked to the nature of national healthcare systems, as well as investment in and expenditure on cancer treatment[106].

Overall, the European landscape with regard to cancel incidence and mortality is a varied one, with the most significant variation being the variation between individual cancers. Although the overall mortality rate appears to be on the decline, the rising incidence and relatively high mortality rates across particular forms of cancer mean that the set of conditions is likely to remain a significant European public health challenge for the years to come. This in turn means that securing availability of cancer products is and will be of particular importance.

8.4.3 Availability problems and problem drivers

The following sections outline the availability problems concerning cancer products. As is the case for medicinal products in general, the availability problems associated with cancer products include:

- products not being authorised;
- products being authorised but not marketed; and
- products being marketed, but still (temporarily) unavailable.

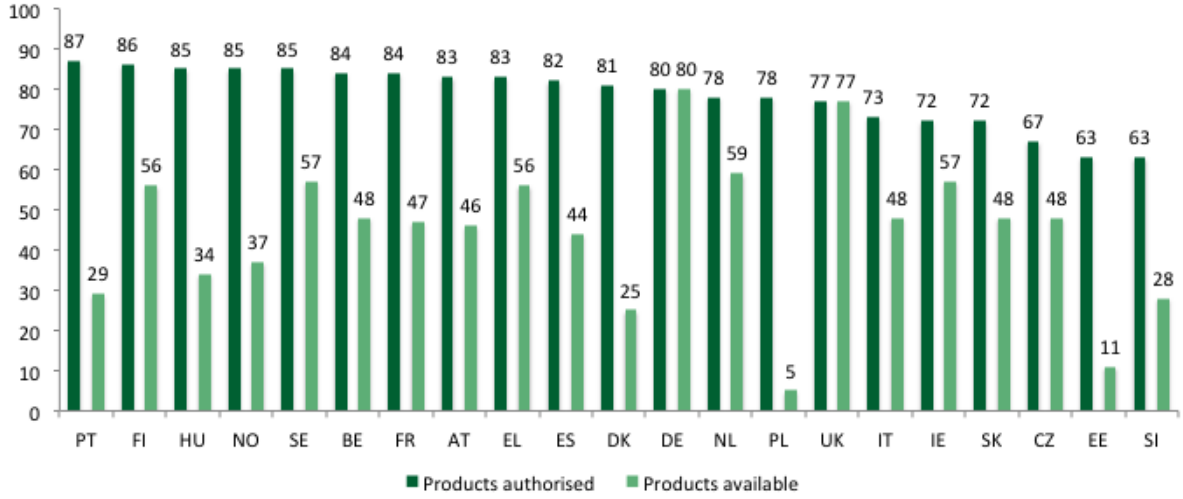
The following sections outline some of the availability problems associated with cancer products.

Authorisation and marketing

As in the case of medicinal products in general, there is a variation in terms of the number of products authorised and marketed in individual Member States. The 2009 Comparator Report on Patient Access to Cancer Drugs in Europe uses the EFPIA database on time-delays in market access to show, among others, the number of cancer products authorised in individual Member States between 2003 and 2006 and products available as of 2007 (defined here as products where pricing and reimbursement procedures have been completed and products are available to patients in pharmacies and hospitals).

[106] Wilking N. and Jönsson, B. (2005), 'A pan-European comparison regarding patient access to cancer drugs', archive.eahp.eu/content/download/25383/.../SpecialReport76-77.pdf

Figure 23: Availability of authorised products



Source: Wilking N., Jönsson, B. and Högberg, D. (2009). \Comparator Report on Patient Access to Cancer Drugs in Europe'

As one can see in the figure above, there are variations in the number of products authorised, as well as those available to patients, although there is no clear pattern with regard to size of individual Member States. Significantly, the variations in the number of products actually available to patients are much greater. This can be attributed to the fact that since 2005 cancer products are authorised through the centralised procedure, while the price and reimbursement procedures and time taken for those to be completed can be seen as a source of the differences in availability levels.[107]

Overall, according to stakeholder consultation and existing literature, the authorisation process and subsequent marketing of products is not seen as a particular obstacle to availability of cancer products. The exception is Malta, where the NCA noted that there is an insufficient number of cancer products for hospital use authorised and marketed in the country, however it is not clear whether this is a result of the market size or other factors (such as higher distribution costs). As mentioned above, studies looking at access to cancer products attribute the limited or delayed availability of these products at this stage in process primarily to the time-consuming pricing and reimbursement procedures, as well as the uptake of innovative cancer products[108]. It is important to note that existing information on authorised and marketed products does not allow to draw conclusions about availability of individual active substances. However, given that many of the products discussed in the above section are likely to be originator products containing new active substances, limited availability of such products on some markets is likely to have public health implications.

In addition to non-authorisation and non-marketing of products, there are also indications of temporary availability problems due to shortages and supply disruptions related to products that are authorises and marketed. These are discussed in more detail in the next section.

[107] Wilking N., Jönsson, B. and Högberg, D. (2009), 'Comparator Report on Patient Access to Cancer Drugs in Europe', http://eu.vocuspr.com/Newsroom/ViewAttachment.aspx?SiteName=ESMO&Entity=PRAsset&AttachmentType=F&EntityID=103275&AttachmentID=f60eb64a-e480-48ec-a5ca-b5c9163d3b70

[108] Wilking N., Jönsson, B. and Högberg, D. (2009), 'Comparator Report on Patient Access to Cancer Drugs in Europe, and Wilking N. and Jönsson, B. (2005), 'A pan-European comparison regarding patient access to cancer drugs'

Shortages and supply disruptions

A number of consulted availability problems and shortages specifically of cancer products were identified during the consultation and literature review:

- In Austria, oncological products are seen as affected by supply chain-related shortages more than other products
- In Hungary, oncological products are a product group identified as being particularly prone to unavailability due to problems with sourcing active ingredients or logistical issues
- In Ireland, shortages of specialised products, such as the anti-cancer product Caelyx were encountered
- In Lithuania, availability problems have been identified with anticancer medicines without suitable substitutes, such as fluorouracil or tamoxifen
- Poland faced shortages of cytotoxic anti-cancer products (etoposide, cisplatin, fluorouracil, doxorubicin, epirubicin, gemcitabine) due to manufacturing problems at a Sandoz site in Austria[109]

All the shortages outlined above can have serious public health implications, since they are likely to have an impact on the treatment of cancer patients. The following box outlines an example of a Carmustine shortage encountered in Italy in 2001:

Carmustine shortage in Italy

Carmustine is an "essential high-dose therapy drug" for stem cell transplantations in patients with lymphoma. In May 2011 an order of 100 failed to be delivered to the National Cancer Institute of Aviano, Italy. At that point nine patients were in the course of a treatment programme that was to include a bone marrow transplant in August of that year. The medical staff had to decide to lengthen the treatment period for patients responding well to treatments in preparation for the transplant and use experimental alternative products for remaining patients were prolonging the treatment programme could have had detrimental results.

Source: Tirelli, U., Berretta, M., Spina, M., Michieli, M. and Lazzarini, R. (2012), 'Letter to the Editor - Oncologic drug shortages also in Italy', *European Review for Medical and Pharmacological Sciences* 138 2012; 16: 138-139

Such availability problems are not unique to cancer products, although the stakeholder consultation has shown that cancer products were often mentioned as an example of a group of products affected by shortages. This can be explained by the fact that that some cancer products are likely to be produced at fewer manufacturing sites and in the cases of more rare conditions, in lower volumes, making the supply susceptible to disruptions. These disruptions can in turn become particularly problematic where there are few substitute products.

[109] The Pharma Letter (2012), 'Cancer Drug Shortages persist in Poland', 26 April 2012, http://www.thepharmaletter.com/file/112884/cancer=-drugs-shortages-persist-in-poland.html

8.4.4 EU Legal framework

The key aspect of the current EU legal framework concerning cancer products is the Annex of Regulation No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. The regulation specifies that products containing new active substances with a cancer indication are to be authorised by the community. This effectively specifies that all originator cancer products are authorised using the CMA procedure in all the Member States, which in turn helps explain the fact that differences in the number of authorised products in individual Member States are relatively small.

Another important element of the EU legislative framework is the use of exceptional circumstances clause set out in Article 22 of Directive 2001/83/EC. This allows for the granting of central marketing authorisation without complete efficacy and safety data if a given condition is rare or if there are ethical considerations not allowing for sufficient testing. This authorisation procedure has been used for a number of anticancer products[110]. The fact that the authorisation process for cancer products is not seen as particularly problematic suggests that these procedures and their functioning are fit-for-purpose. However, as set out in the previous section, the main availability problem appears to be the placing of authorised products on the market and ensuring their constant availability, which cannot be addressed by provisions such as Article 22.

8.4.5 Conclusions

Compared to other groups of medicinal products, availability problems related to cancer products generally occur after the authorisation stage. The EU provisions specifying that new cancer products are to be authorised through the CMA procedure appear to have been effective in ensuring that authorisation of the products is not seen as problematic. Where availability problems appear to occur is at the pricing and reimbursement stage and at the point of uptake by national healthcare systems and medical professionals, although these issues are outside of the scope of the study. Another set of significant availability problems concerns shortages and disruptions where cancer products are identified as one of the categories of products most commonly affected.

Existing tools aiming at ensuring availability and used for cancer products, such as Article 22, focus solely on the authorisation stage and therefore other solutions need to be considered. It is therefore important to examine provisions which aim to ensure the marketing of products and the continuous supply of products, such as Article 81 of Directive 2001/83/EC, from the point of view of their effectiveness in ensuring the availability of cancer products. In particular, it would be important to decide whether there are grounds for addressing shortages and disruptions relating to cancer products as a issue from shortages and disruptions concerning medicinal products in general and, as a result, whether specific mention should be made of these products in such provisions.

[110] Wilking N., Jönsson, B. and Högberg, D. (2009), 'Comparator Report on Patient Access to Cancer Drugs in Europe' and Wilking N. and Jönsson, B. (2005), 'A pan-European comparison regarding patient access to cancer drugs'

8.5 Case study 5: Availability of paediatric medicinal products

Member states	EU27
Interviewees	NCA Interviews Published reports

8.5.1 Background

Paediatric medicinal products are defined as products authorised for paediatric indication, meaning that they are authorised for use in at least one part of the paediatric population, defined in turn as population aged between birth and 18 years[111]. More precise age groups forming the paediatric population include:

- Preterm newborn infants
- Term newborn infants (0-27 days)
- Infants and toddlers (1 month to 23 months)
- Children (2 – 11 years)
- Adolescents (12 – 16 or 18 years)[112]

As of 2006 there are specific EU provisions concerning paediatric products. This is a result of the realisation that the number of medicinal products on the EU market authorised for use in the paediatric population is insufficient[113]. Given the large size of the target group, estimated to account for approximately a quarter of European population[114], such unavailability problems can have a significant public health impact This case study outlines the availability problems relevant to paediatric medicinal products, as well as discusses the legal framework concerning these products.

8.5.2 Availability problems and problem drivers

The following sections outline the availability problems associated with paediatric medicines, as well as the problem drivers.

Authorisation and marketing problems

The main availability problem in the EU and also globally relates to the lack of sufficient number of products authorised with a paediatric indication. A 2010 EMA report on the survey of all paediatric uses of medicinal products in Europe found that between 45% and 65% of products prescribed to patients under the age of 18 were off-label, meaning that the use of these products in a paediatric population was outside the scope of the products' marketing

[111] Regulation (EC) No 1901/2006
[112] EMEA (2006), 'Committee for Medicinal Products for Human Use (CHMP) – Reflection Paper: Formulations of Choice for the Paediatric Population'
[113] See http://ec.europa.eu/health/human-use/paediatric-medicines/index_en.htm
[114] Permanand, G., Mossialos, E. and McKee, M. (2007), 'The EU's new paediatric medicines legislation: serving children's needs?', *Arch Dis Child* 2007;92:808–811. doi: 10.1136/adc.2006.105692

authorisation[115]. This does not necessarily mean that the product is not authorised in the Member State in question (this is often called 'unauthorised' or 'unlicensed' use), but it could be authorised only for use in the adult population. The EMA report recognises two main problems:

- The product which can be used in a paediatric population is not authorised in a given Member States and, as a result, is used as unauthorised in hat Member State
- The product is authorised in a given Member State, but not for the relevant age group and, as a result, used off-label for this group[116]

In both cases, unauthorised use or off-label use in a particular age group may mean that a given product could have reduced efficiency or could bring about adverse reactions in that particular age group[117]. Overall, off-label and unauthorised use of products in a paediatric population could be seen as an indication of unavailability of particular products for a specific population group.

The EMA report reveals a number of variations between off-label use in individual Member States as well as between individual products. Although the information is not easily comparable, the report found that, for instance, in Ireland 15% of products in hospital pharmacies were used off-label in relation to age. By contrast, in Finland 57% of all products were used off-label[118]. Overall, the EMA report suggests that the problem is common across al EU Member States regardless of size.

The therapeutic classes where off-label use is most common include antiarrhythmics, antihypertensives, proton pump inhibitors and H2-receptor antagonists, antiasthmatics, and antidepressants. The EMA report concludes that areas in most need of products authorised for use in the paediatric population include oral contraceptives, gastroenterology (reflux), cardiovascular (hypertension), and respiratory (asthma) and the most affected populations include premature and term neonates, infants, and patients with serious conditions admitted to intensive care units[119].

Problem drivers

Although off-label and unauthorised use suggests that in a given situation a product authorised for paediatric use is not available, the exact nature of the availability problem and the problem driver is not always clear. As noted above, the product can be not authorised for use in a specific population or age group, but used off-label, or a product could not be authorised in a given Member State but used nevertheless. The EMA report generally did not allow us to distinguish between these two instances at EU-level. A Member State where this is possible is Estonia, where out of 31% of unauthorised or off-label prescriptions 29% were for products that

[115] EMA (2010), 'Report on the survey of all paediatric uses of medicinal products in Europe', www.ema.europa.eu/docs/en_GB/.../Report/.../WC500101006.pdf
[116] EMA (2010), 'Report on the survey of all paediatric uses of medicinal products in Europe', www.ema.europa.eu/docs/en_GB/.../Report/.../WC500101006.pdf
[117] See http://ec.europa.eu/health/human-use/paediatric-medicines/index_en.htm
[118] EMA (2010), 'Report on the survey of all paediatric uses of medicinal products in Europe', www.ema.europa.eu/docs/en_GB/.../Report/.../WC500101006.pdf
[119] EMA (2010), 'Report on the survey of all paediatric uses of medicinal products in Europe', www.ema.europa.eu/docs/en_GB/.../Report/.../WC500101006.pdf

did not have paediatric information in the summary of product characteristics, while 0.05% were for products that were not authorised for marketing in the country[120]. Although this is only a single Member State example, it suggest that the availability problems refer primarily to products not being authorised for paediatric use, rather than products not authorised in individual markets at all.

More broadly, the commonly identified sources of the limited number of products being authorised for paediatric use are:

- small number of paediatric clinical trials, in particular those involving neonates, meaning that there Is little data to inform research and development of paediatric products; and
- small and fragmented market for paediatric products, especially given the ability to use off-label adult products[121].

According to existing literature, the main reasons for the small number of paediatric trials include ethical considerations related to exposure of children to new molecules, as well as the perceived length, difficulty, and cost of such trials[122]. The second problem driver, namely the perceived small and fragmented market for paediatric medicinal products, has been identified as the main source of availability problems concerning paediatric medicinal products in the UK by a UK stakeholder.

The sources of availability problems regarding paediatric products therefore appear to be a combination of practical (ethical) and economic (commercial) considerations. Regulation (EC) No 1901/2006 on medicinal products for paediatric use aims to address these problems. The Regulation and its impact are described in more detail in the following section.

8.5.3 EU Legal framework

According to the EMA, the objective of the Paediatric Regulation is to improve children's health by fostering research, increasing availability of paediatric medicines, and increasing information on paediatric medicines. It aims to achieve the above without unnecessary studies in children and delaying products' authorisation for adults[123].

The key elements of the Paediatric Regulation include the:

[120] EMA (2010), 'Report on the survey of all paediatric uses of medicinal products in Europe', www.ema.europa.eu/docs/en_GB/.../Report/.../WC500101006.pdf
[121] EMA (2012), '5-year Report to the European Commission: General report on the experience acquired as a result of the application of the Paediatric Regulation', http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf
[122] EMA (2012), '5-year Report to the European Commission: General report on the experience acquired as a result of the application of the Paediatric Regulation'; Choonara, I. (2000), 'Clinical trials of medicines in children', *BMJ* Volume 321 4 November 2000; Bavdekar, SB. And Goktay NJ. (2005), 'Unlicensed and Off-label Drug Use in Children', *Journal of Postgraduate Medicine.* December 2005 Vol, 51 Issue 4
[123] EMA Regulatory incentives: Experience from European Medicines Agency – Presentation

- Paediatric Investigation Plan (PIP) outlining the research programme necessary to generate data necessary for paediatric authorisation; and
- a system of obligations and rewards aiming to incentivise marketing authorisation holders to authorise products for paediatric use.

The Regulation also established the Paediatric Committee responsible for assessing the PIPs and providing opinions on decisions related to the PIP.

Under the Regulation, all new marketing authorisations need to include results of the studies outlined in the PIP except where these have been waived for a specific product or a class of products. The grounds for a waiver include lack of efficacy or safety in paediatric population, the occurrence of a given condition only in the adult population, or lack of significant therapeutic benefit in that population. In addition, deferral can be used to allow for marketing authorisation for an adult population only before completion of the PIP research[124].

Compliance with the PIP (only if studies are conclusive and results of studies are included in product characteristics and patient leaflets) results in a six-month supplementary protection certificate extension (essentially a patent extension) for non-orphan products and a two additional years of market exclusivity for orphan products. This process also applies in the case where new indications, new routes of administration, or new formulations are authorised for already authorised products. Finally, a ten-year data exclusivity period can be awarded for off-patent products authorised under the Under a Paediatric Use Marketing Authorisation (PUMA) scheme[125].

The Regulation therefore provides incentives to conduct studies necessary for authorising a product for a paediatric indication, by making it more economically attractive for pharmaceutical producers to authorise their products for use in paediatric populations. This is particularly significant, as it is the only set of European provisions, which directly addresses the economic drivers of availability.

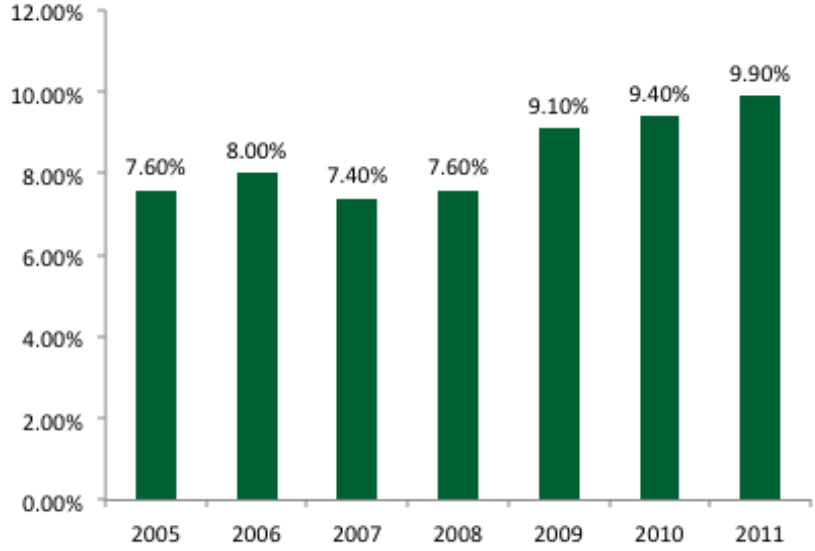
The Regulation also includes other specific provisions relevant to availability:

- Article 35 allows for a marketing authorisation to be transferred to an interested third party (when the marketing authorisation holder has benefited from rewards or incentives under Article 36, 37 or 38, and these periods of protection have expired) helping to prevent the discontinuation of products
- Article 33 states that In the case of products that have already been marketed with other indications, the marketing authorisation holder shall place a product on the market taking into account the paediatric indication within two years of the date on which the paediatric indication is authorised
- Article 36(3) makes the extension of the supplementary protection certificate conditional on product being authorised in all Member States

[124] EMA Regulatory incentives: Experience from European Medicines Agency – Presentation
[125] EMA Regulatory incentives: Experience from European Medicines Agency – Presentation

The 2012 EMA report reviewing the five years of implementation of the Regulation concluded that progress have been made with regard to the objectives of the Regulation during this period. According to the report, in 2006 around 75% of centrally authorised medicinal products were relevant to the paediatric population, but only 34% had a paediatric indication. Since that point (until the end of 2011), PIPs were completed for 29 new products, 13 new products, 30 new indications, and 9 new pharmaceutical forms were authorised for paediatric indication, and 12 products benefited from rewards set out in the Regulation[126]. Although it is difficult to isolate the potential impact of the Regulation in the above figures, the evolution on the number of paediatric trials undertaken, shown below, does suggest that the Regulation is having a positive impact.

Figure 24: Number of paediatric trials as a proportion of the total number of trials



Source: 5 year report EMA (2012). EMA/428172/2012 - 5-year Report to the European Commission: General report on the experience acquired as a result of the application of the Paediatric Regulation

Although there are indications that the Regulation is contributing to addressing the problem drivers behind limited availability of paediatric medicinal products, it is important to note that rising number of clinical trials and authorisation of products does not necessarily mean that suitable products are available in pharmacies and hospitals. Evidence of widespread off-label and unauthorised use in recent years, as well as the fact that stakeholders in Member States such as the UK identify paediatric products as one of the problematic areas in terms of availability, suggests that there is still significant scope for progress. Nevertheless, it appears that the Paediatric Regulation is helping to move towards increased availability. One indication of this are the responses to the 2012 consultation on the Regulation, where majority of the

[126] EMA (2012), '5-year Report to the European Commission: General report on the experience acquired as a result of the application of the Paediatric Regulation', http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf

respondents expressed the opinion that the Regulation helped paediatric development become an integral part of product development[127].

This is not the say that the Regulation has not been met with some criticism. Permanand et al. note that while in the US a similar process has been seen as very effective in generating clinical data and prescribing information, lower prices in the EU could mean that the overall impact may be lower, since the resulting revenues are likely to be lower. At the same time, such incentives could also lead to research on products that may not meet the key needs of the paediatric population (i.e. by focusing on anti-hypertensive products, where hypertension is a rare cause of mortality in children). More generally, the authors of the article fear that the Regulation is overly focused on bringing products to market rather than meeting the needs of patients[128].

Some of the responses to the 2012 consultation paint a similar picture. Although, as noted above, the Regulation is viewed positively and considered an important step forward, some respondents are concerned that the Regulation can result in paediatric development being dependent on adult development rather than responding to paediatric needs[129].

However, at this point it is too early to make a full assessment of the extent to which the Regulation is not only bringing products to the market, but also meeting the patients' needs.

8.5.4 Conclusions

Literature review and stakeholder consultation suggest that the small number of products with paediatric indication in the EU market constitutes an important availability problem. Although this does not necessarily mean that the active ingredients in question are not present on the EU markets, their unauthorised or off-label use in paediatric population comes with public health risks. The Paediatric Regulation is an instrument aiming to address this problem. To date the Regulation appears to have had a positive impact on authorisation of products for paediatric use, although it is still too early to assess its broader public health impact.

More broadly, the system of rewards and incentives present in the Paediatric Regulation is generally viewed as effective in encouraging the authorisation of products with paediatric indications and enhancing availability. Some of the consulted stakeholders suggested that such measures could be used to improve availability in other problematic areas, such as small markets. It is however important to note that such a solution would require a PIP equivalent for other types of products in order to link rewards to availability. In addition, it is not clear whether the US and EU experiences concerning paediatric products would translate to other product groups.

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[127] European Commission (2013), 'General report on the experience acquired as a result of the application of the Paediatric Regulation - Summary of the replies to the public consultation', http://ec.europa.eu/health/files/paediatrics/2013_pc_paediatrics/2013_paediatric_report_summary.pdf

[128] Permanand, G., Mossialos, E. and McKee, M. (2007), 'The EU's new paediatric medicines legislation: serving children's needs?', *Arch Dis Child* 2007;92:808–811. doi: 10.1136/adc.2006.105692

[129] European Commission (2013), 'General report on the experience acquired as a result of the application of the Paediatric Regulation - Summary of the replies to the public consultation', http://ec.europa.eu/health/files/paediatrics/2013_pc_paediatrics/2013_paediatric_report_summary.pdf

8.6 Case study 6: Availability of herbal, homeopathic and anthroposophic medicinal products

Member states	EU27
Data sources	Consultation with industry organisations (ECHAMP, EUCOPE, AESGP) Published reports and legislation

8.6.1 Background

This case study looks at the availability of herbal medicinal products, as well as homeopathic and anthroposophic products. These are three distinct product groups regulated through distinct provisions. In the case of homeopathic products, regulation is primarily through Articles 14 and 16.2 of the Directive 2001/83/EC (described in more detail in the next sections), while in the case of herbal medical products these involve the simplified procedure introduced in Directive 2004/24/EC on Traditional Herbal Medicinal Products (THMPD). The three product groups do however share some attributes:

- individual manufacturers often produce both herbal medicinal products and homeopathic products;
- it is widely recognised that national medical traditions differ with regard to how these product groups are perceived; and
- in the case of herbal medicinal products and homeopathic products, respective industry organisations note that there are availability problems across the EU linked to the differences in national approaches as well as ineffective or inconsistent application of European provisions.

This case study aims to investigate in more depth the potential availability problems concerning these products. It is important to note that the case study looks at the availability of the products as medicinal products for human use, rather than more broader availability on the market, for instance as food supplements.

Definitions

Herbal products are defined by Directive 2004/24/EC on Traditional Herbal Medicinal Products (THMPD) as products "exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations"[130]. The Directive defines *traditional* herbal medicinal products as products fulfilling the following criteria:

- they have indications exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment;

[130] Article 1 of Directive 2004/24/EC on Traditional Herbal Medicinal Products

- they are exclusively for administration in accordance with a specified strength and posology;
- they are an oral, external and/or inhalation preparation;
- the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience[131].

Homeopathic products are defined as products "prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States"[132]. This means, in practice, that they are products consisting of diluted doses of substances, which in larger quantities would create the symptoms in a healthy person.

Anthroposophic medicinal products are products that use natural substances and require "heat, rhythmic preparation and potentising methods"[133]. It is important to note that regulatory framework concerning anthroposophic products is more fragmented and, as a result, there are no harmonised definitions of such products across the EU, nor systematic data on such products. This means that the focus in the sections below will be primarily on herbal and homeopathic products, however, where information is available, anthroposophic products will also be considered.

Market size

According to AESGP (Association of the European Self-Medication Industry), the total market size for herbal medicinal products[134] was approximately EUR 6bn in 2010[135], while ECHAMP (European Coalition on Homeopathic and Anthroposophic Medicinal Products) estimated the total sales (at ex-factory prices) of homeopathic products in the same period to be EUR 1,035bn[136]. Although this constitutes less than one percent of the EU pharmaceutical market[137], sales of such products remain significant and warrant an exploration of the availability issues associated with these product groups.

8.6.2 Availability problems

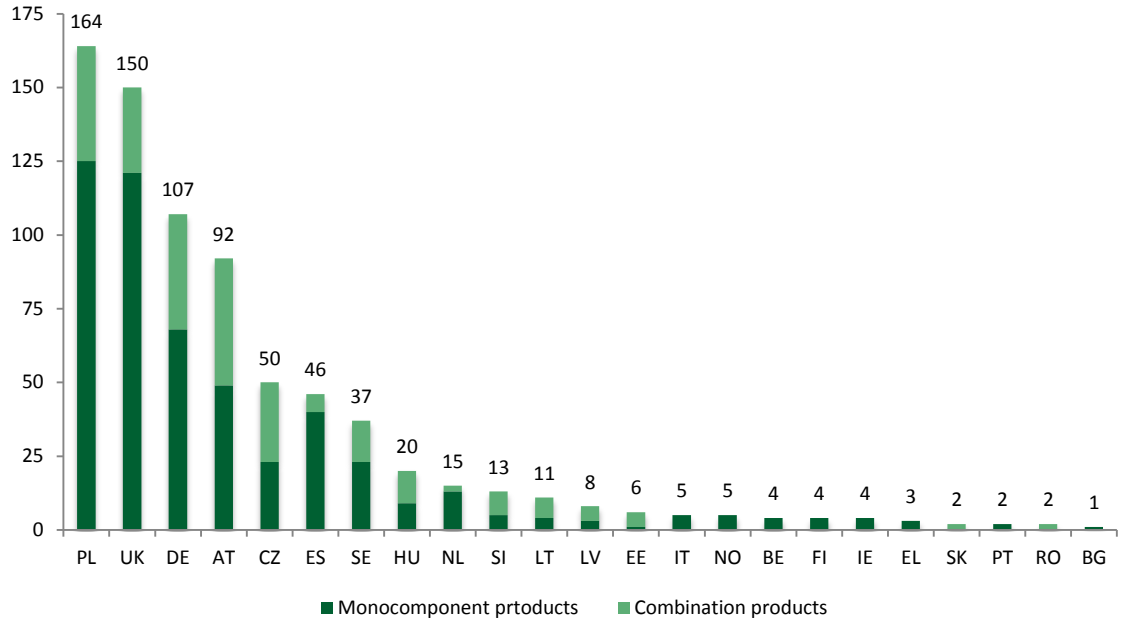
The following sections outline existing evidence concerning the availability of herbal medicinal products, as well as homeopathic and anthroposophic products.

[131] Article 1 of Directive 2004/24/EC on Traditional Herbal Medicinal Products
[132] Article 1 of Directive 2001/83/EC
[133] See http://www.echamp.eu
[134] Where terms "herbal medicinal products" or "homeopathic medicinal products" are used these are meant to describe products authorised explicitly as medicinal products
[135] Presentation of the Chair of the AESGP Herbal Medicinal Committee
[136] ECHAMP (2012), 'The Availability of Homeopathic and Anthroposophic Medicinal Products in the EU'
[137] EFPIA (2012), 'The Pharmaceutical Industry in Figures – Key Data 2012'

Availability of herbal medicinal products

The key issue noted by industry stakeholders with regard to the availability of (traditional) herbal medicinal products is the limited use of the simplified procedure (introduced in the Directive 2004/24/EC). This is illustrated in the figure below, provided by AESGP:

Figure 25: Number of registrations of traditional herbal medicinal products under Directive 2004/24/EC until December 2011



Source: AESGP

The above figure shows that the differences in the number of registrations do not necessarily correspond to the size of the national market. Poland, UK, and Germany are three of the larger EU markets, but there were also considerably more registrations in Austria and Czech Republic than, for instance, in Italy or France (although not included in the above figure, according to AESGP there were in total four registrations in France).

As industry stakeholders point out, however, there are differences in the way individual Member states approach herbal products and one can also expect that the demand for herbal products may not necessarily correspond to the sizes of individual markets. As noted by the WHO[138], in 2002 (prior to the establishment of the simplified registration procedure), Germany held the largest share of the European herbal medicinal product market with 39% of the market, followed by France (29%), Italy (7%), Poland (6%) and the UK (6%). Although these are all large Member States, the fact that the market share in France and Germany is more than triple that of the remaining five countries, suggests that herbal products play a much larger role in these two Member States.

[138] See http://apps.who.int/medicinedocs/en/d/Js4950e/1.html#Js4950e.1.1

When comparing these figures to the pattern in the number of registrations shown above, one can notice potential discrepancies. The size of the market for herbal medicinal products in Germany is not reflected in the fact that the number of registrations in Poland and the UK (both markets with potentially substantial demand for such products, but not nearly as high as in Germany) is considerably higher, More significantly, the low number of registrations in France, compared with the fact that total demand for such products was second only to Germany, suggests that there may be potential availability problems associated with few registrations in France. To a lesser extent this may also be the case in Italy.

More broadly, it is important to note that the above sections interpret availability strictly within the context of the procedure introduced in the THMP Directive. This means that in some Member States (such as France and Italy) where there may be demand for herbal medicinal products, some products might not be registered through the THMP procedure. However, this does not necessarily imply that the products are not on the market, as they may be available as, for instance, food supplements. Finally, it is important to also note that availability issues concerning herbal medicinal products have not been recognised by other stakeholder groups. This suggests that the potential availability issues are unlikely to be acute ones. Nevertheless, the substantial disparity between the number of registrations warrants a closer examination of potential drivers. These are explored in more detail in Section 3.

Availability of homeopathic and anthroposophic products

With regard to the availability of homeopathic and anthroposophic products, a PwC study commissioned by ECHAMP examined a selection of products in five Member States (Bulgaria, France, Germany, Romania, and Spain) and noted, among others, that:

- There were moderate differences in availability, with most products being readily available in Germany, followed by France and Spain;
- Homeopathic medicinal products with no therapeutic indication are difficult to obtain directly (without ordering), but they can usually be delivered to order;
- There are generally no major issues regarding availability of homeopathic medicinal products for specific symptoms;
- Direct availability (without ordering) of anthroposophic products is generally worse than in the case of other homeopathic products

The above results, although they refer to only a subset of Member States, suggest that there are indeed some differences in availability of these products across the EU. However, as noted by industry stakeholders, and also analogous to herbal medicinal products, there are likely to be national differences in demand for such products.

Generally, according to ECHAMP data, sales of homeopathic and anthroposophic products as a percentage of total pharmaceutical market and per inhabitant are higher in France and Germany than in Bulgaria and Romania, two of the new Member states investigated in the aforementioned PwC study. Taking this to reflect the demand in these Member States, this would be consistent with the findings concerning availability, suggesting that Member States with higher demand for such products would also be ones where such products are more

available. On the other hand, on some metrics, the homeopathic market in Bulgaria appears to be larger in relative terms than that of Spain (i.e. when looking at homeopathic product sales as a percentage of the pharmaceutical market or looking at the number of homeopathic prescribes per capita). This, coupled with the fact that availability appears to be more problematic in Bulgaria than Spain, suggests that limited availability could result in some of the demand for such products not being met in some Member States[139].

At the same time it is important to note that, in general, the ECHAMP study did not find availability in all Member States to be particularly problematic, with the products surveyed generally being available when ordered in advance, meaning that they were both authorised and marketed. Secondly, as in the case of herbal medicines, other stakeholders consulted as part of the study (i.e. National Competent Authorities across the EU) have not raised the issue of the availability of homeopathic products.

Finally, it is also important to note that availability and sales (used here as a proxy for demand), can be interdependent concepts, with lower perceived demand (i.e. lower sales) potentially resulting in unavailability (since the manufacturers, or regulators, could place lower value on getting such products on the market), but also lower availability (due to other factors), potentially resulting in lower sales, which can then be misinterpreted as lower demand. Therefore, data such as number of homeopathic prescribers is important in triangulating such findings. Given that in the case of homeopathic products, this data shows Bulgaria as a Member State with more demand for homeopathic products than Spain (or even France and Germany), it is valuable to explore potential drivers of unavailability.

8.6.3 EU Legal framework

For both herbal medicinal product and homeopathic products, industry associations note that the existing regulatory procedures are either ineffective or are incorrectly applied, contributing to unavailability problems. These potential problem drivers are outlined below.

Traditional herbal medicinal products

The 2004 Directive established the simplified traditional-use registration procedure, which does not require extensive documentation given that there is sufficient documentation of the medical use of the product in the previous 30 years, including 15 years within the EU[140]. The Committee for Herbal Medicinal Products (HMPC) at the European Medicines Agency (EMA) supports this process.

However, as noted by AESGP, there are a number of issues associated with this procedure:

- there are long registration times in some Member States (ranging from 9 to 32 months), which are seen as being the result of limited resources, low prioritization, and lack of familiarity with herbal products in some national agencies; and

[139] ECHAMP (2012), 'The Availability of Homeopathic and Anthroposophic Medicinal Products in the EU'
[140] See http://ec.europa.eu/health/human-use/herbal-medicines/index_en.htm

- access conditions in some Member States are viewed as restrictive, including high fees (same as for chemical entities), different advertising rules, and other restrictions in selected Member States (age or pack size restrictions).

The above points reflect the industry position, but they do show that there are differences in Member State approaches, which could explain in part the pattern of registrations shown in the figure above. Although the simplified procedure is a national one, allowing for variation in Member State approaches, the above points suggest that the current practices may fall short of the new procedure's goals of facilitating the movement of traditional herbal medicines and harmonising the national rules, with a potential bearing on the availability of these products. It needs to be emphasised again that these potential shortcomings relate to delays and small number of products authorised as traditional herbal medicinal products. This does not necessarily mean that the products are not available on the market (for instance as food supplements). Nevertheless, according to the definition of availability used in the study, these delays could be seen as availability problems as the products in question are not available in a pharmacy setting.

Homeopathic products

As in the case of herbal medicinal products, a simplified procedure is in place for homeopathic products (as outlined in Article 14 of Directive 2001/83/EC), but industry stakeholders note problems with this procedure. These include in particular:

- long waiting time to authorise products (12-25 months), attributed to the lengthy administrative procedures;
- perceived disproportionate burden associated with the decentralized procedure provided for in Article 13 of the Directive, resulting in it being very rarely used;
- inconsistent application of Article 16.2 of the Directive (allowing a Member State to adopt specific rules concerning homeopathic products outside of those covered in the simplified procedure in accordance of homeopathy principles practiced in that Member State). As a result in only a selection of Member States where it has been adopted have products been registered through this procedure.

As in the case of herbal medicinal products, these findings suggest that the existing legislative framework for homeopathic products may fall short of simplifying procedures and introducing more harmonization across the EU for these products.

It is important to also keep in mind that homeopathic products are not a homogenous group. The simplified procedure set out in Art. 14(1) concerns products with no therapeutic indication, with concentrations lower than 1:10,000 and does not cover injectables. Producers aiming to introduce such products on the market therefore need to rely on Member State implementation of Article 16(2), which, as noted above, remains fragmented across the EU. As a result, there is no clear and consistent EU registration procedure for homeopathic products not covered under Article 14(1) (products with indication, or higher concentration products). This in turn means that some products effectively cannot be registered as homeopathic products in some markets, or need to be registered as products without indication (given that they are not injectables and do

not exceed the aforementioned concentration levels). It is important to note, however, that at the moment only few such products exist.

8.6.4 Conclusions

The analysis shows that even taking into account the demand and use of (traditional) herbal medicinal products and homeopathic products, in some Member States fewer such products are registered or registration is more time consuming leading to (temporary) unavailability. Although availability problems concerning these groups of products have not been identified by the NCAs or other non-industry stakeholders, the implementation of existing EU provisions concerning these products could be further improved. These provisions aim to simplify the authorisation process and ensure more harmonisation across the EU, but the evidence collected as part of this case study suggests that more progress could be made in this direction. Given the demand for such products, there appears to be a need for further action in this area, which, according to consulted stakeholders, should focus on ensuring that the process of authorisation of herbal medicinal products and HAMPs is more consistent, both with the text of the existing provisions and between Member States. The consulted stakeholders did not however point to a particular good practice example, suggesting that at the moment there is not blueprint for an optimal approach to authorising such products.

9.0 Appendix II: Methodological notes

The following section outlines the main methodological considerations related to study tasks undertaken to date.

9.1 Scoping Literature Review

The scoping literature review aimed to develop a good understanding of the range of issues that have bearing on the availability of pharmaceuticals in the EU. This in turn informed the conceptual understanding of the problem drivers and of the potential impact of the pharmaceutical acquits on the availability of medicinal products. The literature was also used to extract relevant secondary data that supported the results of the secondary data analysis and stakeholder consultation.

Since information relevant to availability of medicinal products is likely to be found primarily in grey literature, the literature search focused primarily on an Internet search using the two main keywords in English, French, and German ("availability", "medicines", "medicinal products", "Verfügbarkeit", "Arzneimittel", "disponibilité", "médicaments", "produits médicaux", "produits pharmaceutiques"). In addition, consulted stakeholders have also been asked for additional sources relevant to the study. The list of references is presented in Appendix II.

9.2 Secondary Data Analysis

The analysis of secondary data on availability is based primarily on three types of data sources:

- EMA Database;
- HMA Mutual Recognition Database; and
- National Databases

Whereas the EMA and HMA databases show total number of products authorised through those procedures, they do not cover national authorisations. At the moment, there is no other source of comparable data on authorised products that would cover the EU27. EudraPharm is one initiative aiming to do that, but despite recent updates it still does not include national authorisation data. Similarly, Common European Drug Database (CEDD) covers only a subset of Member States. To that end, national databases have been analysed in order to fill the gaps and present a comprehensive picture of availability.

Analysis of national datasets

Websites of all competent authorities have been screened to identify available data. In addition, we have used consultation with competent authorities to clarify data availability for individual countries. This first screening yielded a number of challenges:

- Data on authorisations is available in different formats – these include online databases, which can be queried, downloadable data files, .pdf documents, and printed lists;

- Content of datasets differs substantially in terms of information included - some datasets include only name of product and reference number, others provide considerably more information, for example on type of product, API, ATC code, and even pricing and reimbursement data; and
- Level of aggregation differs between databases - in some Member States datasets include only individual brand names, in other Member States each packaging variation has its own entry.

The countries included in analysis where ones where databases of authorised products were possible to analyse or where information could be effectively extracted from documents in other formats. These countries include Belgium Bulgaria, Cyprus, Czech Republic, Germany, Denmark, France, Hungary, Ireland, Iceland, Malta, Netherlands, Norway, Poland, Portugal, Slovenia, Slovakia and Sweden.

Since the EMA dataset presented authorisation data by individual brand names, and so did selected national databases (i.e. Bulgaria and Norway), the choice was made to focus on **unique products** and disregard variations in, for instance, pack sizes. This also avoids generating misleading results if some national databases contain more disaggregated records than others.

A number of methods were used to identify unique products in national databases. These included:

- Using reference numbers or registration numbers – often registration numbers include a unique identifier and a part signifying variation, which allows to analyse unique products;
- Using brand names and authorisation dates – this allows to eliminate multiple authorisation instances of a single product (usually packaging variations);
- Using products names.

The initial scope of analysis (presented in Section 3.1) was on the total number of products authorised. Where such data was available, information for subsets of country was also analysed by type of product (OTC/prescription) and ATC code in Sections 3.2 and 3.3. Given limited availability of such information in national databases, this data was supplemented by findings from stakeholder consultation.

In some cases (Germany and Slovakia), it was not possible to effectively identify unique entries for all type of authorisations and average numbers of duplicate entries for EMA and MRP procedure authorisations were used to estimate the number of unique products authorised nationally.

Products authorised but not marketed

The second aspect of the analysis is the investigation of products that are authorised but not marketed. In some cases national databases of authorised products provide information on marketing of products. These data, together with information provided by stakeholders

interviewed as part of the stakeholder consultation, provided a broad overview of the proportion of products marketed in a selection of countries (Czech Republic, France, Iceland, Ireland and Latvia). To supplement this analysis, we will explore the use of wholesalers' lists.

9.3 Stakeholder Consultation

Stakeholder consultation consisted of interviews with two main groups:

- National Competent Authorities; and
- European-level stakeholder organisations.

Where requested by stakeholders, we have allowed for stakeholders to complete a questionnaire based on the interview guide and provide it by email. We have consulted **34 stakeholders** in total. It is important to note that despite repeated requests a small number of NCAs did not respond to our questions. Although this potentially limits the comprehensiveness of the study, it is likely that authorities that did not respond to the consultation request do not experience substantial availability problems or had little input to provide in response to the specific questions. We have ensured that all NCAs were aware of the consultation early in the study through a presentation at the EMA's CMDh committee.

9.4 Legislation Screening

In order to identify and examine a comprehensive list of provisions of the EU pharmaceutical legislation having a bearing on availability of medicinal products for human use, we have screened all the relevant EU pharmaceutical legislation as per the EudraLex compilation of Pharmaceutical Legislation[141]. We have found provisions relevant to availability in the following EU legislation:

- Directives:
    - Directive 2001/83/EC
    - Directive 2011/62/EU (amending Directive 2001/83/EC)
    - Directive 2010/84/EU (amending Directive 2001/83/EC)

- Regulations:
    - Regulation (EC) No 726/2004
    - Council Regulation (EC) No 297/95
    - Regulation (EC) No 141/2000
    - Commission Regulation (EC) No 507/2006
    - Regulation (EC) No 1901/2006

The key words used to aid legislation screening included:

- Availab*

[141]The screening of EU legislation is based on EudraLex - Volume 1 - Pharmaceutical Legislation Medicinal Products for Human Use (http://ec.europa.eu/health/documents/eudralex/vol-1/index_en.htm)

- Suppl*
- Offer
- Access
- Plac*
- Delay
- Prompt
- Immediate*
- Benefit
- Compassion*
- Parallel

10.0 Appendix III: References

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11.0 Appendix IV: Stakeholders Consulted

Table 6: National Competent Authorities

Country	Organisation	Status
Austria	AGES-PharmMed LCM (www.ages.at)	Completed
Belgium	Agence Fédérale des Médicaments et des Produits de Santé (www.fagg-afmps.be)	Completed
Bulgaria	Bulgarian Drug Agency (www.bda.bg)	Did not respond
Croatia	HALMED Agency for Medicinal Products and Medical Devices (http://www.almp.hr)	Completed
Cyprus	Ministry of Health - Pharmaceutical Services (www.moh.gov.cy)	Completed
Czech Republic	State Institute for Drug Control (www.sukl.cz)	Did not respond
Denmark	Danish Medicines Agency (www.dkma.dk)	Did not respond
Estonia	State Agency of Medicines (www.ravimiamet.ee)	Completed
Finland	Finnish Medicines Agency (www.fimea.fi)	Completed
France	Agence française de sécurité sanitaire des produits de santé (Afssaps) (www.afssaps.sante.fr)	Did not respond
Germany	BfArM (www.bfarm.de)	Did not respond
Greece	National Organization for Medicines (www.eof.gr)	Did not respond
Hungary	National Institute of Pharmacy (www.ogyi.hu)	Completed
Iceland	Icelandic Medicines Control Agency (www.imca.is)	Completed
Ireland	Irish Medicines Board (www.imb.ie)	Completed
Italy	Agenzia Italiana del Farmaco (www.agenziafarmaco.it)	Completed
Latvia	State Agency of medicines (www.zva.gov.lv)	Completed
Lithuania	State Medicines Control Agency (www.vvkt.lt)	Completed
Luxembourg	Direction de la Santé Villa Louvigny Division de la Pharmacie et des Medicaments (www.ms.etat.lu)	Did not respond
Malta	Medicines Authority Divizjoni Tas-Sahha Bezzjoni Ghar-Regolazzjoni Tal-Medicini (www.medicinesauthority.gov.mt)	Completed
Netherlands	College ter Beoordeling van Geneesmiddelen Medicines Evaluation Board (www.cbg-meb.nl)	Completed
Norway	The Norwegian Medicines Agency (www.legemiddelverket.no)	Completed
Poland	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (www.urpl.gov.pl)	Did not respond
Portugal	INFARMED – Instituto Nacional da Farmácia e do Medicamento Parque da Saúde de Lisboa (www.infarmed.pt/portal/page/portal/INFARMED)	Completed
Romania	National Medicines Agency (www.anm.ro)	Did not respond
Slovakia	State Institute for Drug Control (www.sukl.sk)	Completed
Slovenia	Agencija za zdravila in medicinske pripmocke (www.jazmp.si)	Did not respond
Spain	Agencia Española de Medicamentos y Productos Sanitarios (www.aemps.gob.es)	Completed

Sweden	Medical Products Agency (www.lakemedelsverket.se)	Completed
UK	Medicines and Healthcare products Regulatory Agency (www.mhra.gov.uk)	Completed

Table 7: Other stakeholders

Organisation	Status
European Federation of Pharmaceutical Industries and Associations	Completed
EGA European Generic Medicines Association	Completed
European Association of Euro-Pharmaceutical Companies (EAEPC)	Completed
European Association of Nuclear Medicine (EANM)	Completed
European Association of Pharmaceutical Full-Line Wholesalers (GIRP)	Completed
European Clinical Research Infrastructures Network (ICREL)	Completed
European Coalition on Homeopathic and Anthroposophic Medicinal Products (ECHAMP)	Completed
European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)	Completed
European Organisation for Research and Treatment of Cancer (EORTC)	Completed
European Patients' Forum	Completed
European Self-Medication Industry (AESGP)	Completed
European Vaccine Manufacturers (EVM)	Completed
Pharmaceutical Group of the European union (PGEU)	Completed
Standing Committee of European Doctors (CPME)	Completed

12.0 Appendix V: Stakeholder Consultation Interview Guide

The interview guide to be used in stakeholder consultation is presented below. This guide will also form a basis for the development of case study tools.

Introduction *(optional)*
1) What is your organisation's remit and what is your current role in your organisation?
I. Extent of the problem
2) The first element of the study is to identify availability problems with regard to medicinal products for human use across the EU. Are you aware of such unavailability problems *(in your Member State)*?
3) What are the main issues related to unavailability? • *Products not being authorised?* • *Products being authorised but not marketed?* • *Products marketed but still being unavailable?*
4) Are certain types of products more prone to unavailability than others? • *Differences across therapeutic areas? (e.g. products related to certain conditions which are less common in some Member States than in others?)* • *OTC products compared to prescription products?* • *Generics compared to originators?*
5) Are some markets more prone to unavailability than others? *(only EU-level stakeholders)* • *Smaller markets?* • *New EU Member States compared to EU15?*
6) How is availability affected by parallel trade?
II. Problem drivers
7) What are the main reasons behind the identified availability problems? • *Corporate strategy given size and nature of the market? (i.e. perceived demand, availability of substitutes and generics)* • *Costs associated with the regulatory system? (e.g. reimbursement negotiations, administrative delays, additional administrative costs of maintaining a product on the market such as pharmacovigilance, language and labelling requirements)* • *Supply chain? (e.g., transport and distribution, ordering and stocking)* • *Others?* • *How do these reasons differ across countries? (only EU-level stakeholders)* • *How do these reasons differ across product categories? (differences across therapeutic areas, differences between OTC products and prescription products; between generics and originators)*

III. Baseline scenario
8) What can be done to address the availability of medicinal products?
9) What is the awareness of EU legislation aiming to address unavailability problems? • *New centralised procedure tools in Regulation 726/2004 (Article 14(9) on accelerated assessments, Article 14(7) on conditional authorisations, Article 83 on compassionate use)* • *Measures allowing individual patients to order medicinal products without a market authorisation (Article 5(1) of Directive 2001/83/EC)* • *Measures to authorise to authorise the placing on the market in its territory of a medicinal product authorised in another Member State for justified public health reasons ("Cyprus clause", Article 126a of Directive 2001/83/EC)* • *Measures allowing for the authorisation of generic medicinal products in a Member State in the absence of a reference medicinal product in that Member State.(Article 10(1) of Directive 2001/83/EC)* • *Measures introducing obligations to supply of medicinal products (Article 81 of Directive 2001/83/EC) and invalidating the marketing authorisation if the product is not placed on the market for 3 consecutive years or not present on the market for three consecutive years ("Sunset clause", Article 24 of Directive 2001/83/EC)* • *The Paediatric Regulation (EC) 1901/2006 offered the incentive of an extension of the supplementary protection certificate (essentially a patent extension) only if a product is being marketed in all Member States.* • *The Transparency Directive 89/105/EEC sets out unified administrative procedures for the pricing and reimbursement process and specifies maximum delays for pricing and reimbursement decisions to be made across the EU.* • *Upcoming initiatives (i.e. Anti-falsified medicines)?* • *Others?*
10) Are you aware of such legislation being used *(in your Member State/in a Member State)* to address unavailability problems?
11) Have there been any problems associated with transposition and implementation of relevant EU legislation?
12) What has been the impact of this legislation on availability? • *Are you aware of relevant data or studies?* • *Who could we contact?*
13) Are you aware of other measures being used to address unavailability problems? • *Are you aware of relevant data or studies?*
14) What steps that could be taken to improve the implementation of relevant EU legislation?
15) Are there additional steps that could be taken on EU level of address unavailability problems? • Better implementation of the legal framework? • Other steps?

IV. Closing remarks *(optional)*
16) Can you point us to relevant data sources/persons we can use/consult for this project? • *How complete are these data bases? (e.g. number and type of products covered, number of MSs included, how often are they updated)...* • *How easily can they be accessed/obtained?*
17) Do you have other comments and remarks?

13.0 Appendix VI: Legislation Screening Template

Study on the Availability of Medicinal Products for Human Use

SCREENING OF EU LEGISLATION TEMPLATE

EU Legislation	Relevant Articles	Explanation/Comments from stakeholders
DIRECTIVES		
Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Consolidated version: 05/10/2009).		
Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products.		
Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use.		

EU Legislation	Relevant Articles	Explanation/Comments from stakeholders
(Official Journal L 348, 31/12/2010, p. 74 - 99).		
Directive 2009/53/EC of the European Parliament and of the Council of 18 June 2009 amending Directive 2001/82/EC and Directive 2001/83/EC, as regards variations to the terms of marketing authorisations for medicinal products. (Official Journal L 168, 30/6/2009, p. 33 - 34).		
Directive 2001/20/EC OF the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Official Journal L 121, 1/5/2001 p. 34 - 44).		
Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (Official Journal L 262, 14/10/2003 p. 22 - 26).		
Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (Official Journal L		

EU Legislation	Relevant Articles	Explanation/Comments from stakeholders
91, 9/4/2005 p. 13 - 19).		
Council Directive 89/105/EEC, of 21 December 1988, relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion within the scope of national health insurance systems (Official Journal L 40, 11/2/1989 p. 8 - 11; Finnish special edition: Chapter 15 Volume 9 p. 45; Swedish special edition: Chapter 15 Volume 9 p. 45).		
REGULATIONS		
Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Consolidated version : 20/04/2009, Lithuanian Consolidated version 30/12/2008).		
Amended by **Regulation (EC) No 219/2009** of the European Parliament and of the Council of 11 March 2009 adapting a number of instruments subject to the procedure referred to in Article 251 of the Treaty to Council Decision 1999/468/EC with regard to the regulatory procedure with scrutiny Adaptation to the regulatory procedure with scrutiny - Part Two (Official Journal L 87, 231/3/2009, p. 109 - 154, especially p. 116 - 118, Annex 2.9, where		

EU Legislation	Relevant Articles	Explanation/Comments from stakeholders
Regulation (EC) No 726/2004 is adapted)		
Consolidated version of the **Council Regulation (EC) No 297/95** on fees payable to the European Agency for the Evaluation of Medicinal Products (20.11.2005)		
Commission Regulation (EC) No 540/95, of 10 March 1995, laying down the arrangements for reporting suspected unexpected adverse reactions which are not serious, whether arising in the Community or in a third country, to medicinal products for human or veterinary use authorised in accordance with the provisions of Council Regulation (EEC) No 2309/93 (Official Journal L 55, 11/3/1995 p. 5 - 6).		
Commission Regulation (EC) No 1662/95, of 7 July 1995, laying down certain detailed arrangements for implementing the Community decision-making procedures in respect of marketing authorisations for products for human or veterinary use (Official Journal L 158, 8/7/1995 p. 4 - 5).		
Commission Regulation (EC) No 2141/96, of 7 November 1996, concerning the examination of an application for the transfer of a marketing authorisation for a medicinal product falling within the scope of Council Regulation (EEC) No 2309/93 (Official Journal L 286, 8/11/1996 p. 6 - 8).		

EU Legislation	Relevant Articles	Explanation/Comments from stakeholders
Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (Official Journal L 18, 22/1/2000 p. 1 - 5).		
Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority' (Official Journal L 103, 28/4/2000 p. 5 - 8).		
Commission Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State (Official Journal L 159, 27/6/2003 p. 1 - 23).		
Commission Regulation (EC) No 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93 (Official Journal L 159, 27/6/2003 p. 24 - 45).		
Commission Regulation (EC) No 2049/2005, of 15 December 2005, laying down, pursuant to Regulation (EC) No 726/2004 of the European		

EU Legislation	Relevant Articles	Explanation/Comments from stakeholders
Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises (Official Journal L 329, 16/12/2005 p. 4 - 7)		
Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council (Official Journal L 92, 30/3/2006 p. 6 - 9).		
Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004.		
Regulation (EC) No 1902/2006 of the European Parliament and of the Council of 20 December 2006 amending Regulation 1901/2006 on medicinal products for paediatric use.		
Communication from the Commission - Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (Official		

EU Legislation	Relevant Articles	Explanation/Comments from stakeholders
Journal C 243, 24/9/2008 p. 1 - 12).		
Commission Regulation (EC) No 658/2007 of 14 June 2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No 726/2004 of the European Parliament and of the Council (Official Journal L 155, 15/6/2007 p. 10 - 19).		
Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Note: shall apply from 30 December 2008)(Official Journal L 324, 10/12/2007 p. 121 - 137).		
Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (Official Journal L 334, 12/12/2008 p. 7 - 24).		
Commission Regulation (EC) No 668/2009 of 24 July 2009 implementing Regulation (EC) No 1394/2007 of the European Parliament and of the Council with regard to the evaluation and certification of quality and non-clinical data relating to advanced therapy medicinal products developed by micro, small and medium-sized enterprises (Official Journal L 194, 25/7/2009 p.		

EU Legislation	Relevant Articles	Explanation/Comments from stakeholders
7 - 10).		
Commission Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products. (Official Journal L 348, 31/12/2010 p. 1 - 16).		
MISCELLANOUS		
Council Decision 75/320/EEC, of 20 May 1975, setting up a Pharmaceutical Committee (Official Journal L 147, 9/6/1975 p. 23; Spanish special edition: Chapter 13 Volume 4 p. 102; Portuguese special edition: Chapter 13 Volume 4 p. 102; Finnish special edition: Chapter 13 Volume 4 p. 108 Swedish special edition: Chapter 13 Volume 4 p. 108).		
Council Directive 78/25/EEC, of 12 December 1977, on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products (Official Journal L 11, 14/1/1978 p. 18 - 20; Finnish special edition: Chapter 13 Volume 8 p. 39; Greek special edition: Chapter 13 Volume 7 p. 34; Swedish special edition: Chapter 13		

EU Legislation	Relevant Articles	Explanation/Comments from stakeholders
Volume 8 p. 39; Spanish special edition: Chapter 13 Volume 8 p. 86; Portuguese special edition Chapter 13 Volume 8 p. 86).		
Council Directive 90/219/EEC, of 23 April 1990, on the contained use of genetically modified micro-organisms (Official Journal L 117, 8/5/1990 p. 1 - 14; Finnish special edition: Chapter 15 Volume 9 p. 198; Swedish special edition: Chapter 15 Volume 9 p. 198).		
Council Directive 98/81/EC of 26 October 1998 amending Directive 90/219/EEC on the contained use of genetically modified micro-organisms (Official Journal L 330, 5/12/1998 p. 13 - 31).		
Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (Official Journal L 106, 17/4/2001 p. 1 - 39).		
Council Regulation No (EEC) 1768/92, of 18 June 1992, concerning the creation of a supplementary protection certificate for medicinal products (Official Journal L 182, 2/7/1992 p. 1 - 5; FI and SV special editions: Chapter 13 Volume 23 p. 78; Swedish special edition: Chapter 13 Volume 23 p. 78; CS, ET, HU, LT, LV, MT, PL, SK and SL special editions Chapter 13 Volume 11 p. 200 - 204).		

EU Legislation	Relevant Articles	Explanation/Comments from stakeholders
Commission Communication on parallel imports of proprietary medicinal products for which marketing authorisations have already been granted (Official Journal C 115, 6/5/1982, p. 5).		
Commission Communication on parallel imports of proprietary medicinal products for which marketing authorisations have already been granted. [Update of the 1982 Commission Communication](COM/2003/839 final).		
Commission Communication 94/C 82/04 on the implementation of the new marketing authorisation procedures for medicinal products for human and veterinary use in accordance with Council Regulation (EEC) No 2309/93 of 22 July 1993 and Council Directives 93/39/EEC, 93/40/EEC and 93/41/EEC, adopted on 14 June 1993. (Official Journal C 82, 19/3/1994 p. 4).		
Commission communication on the Community marketing authorisation procedures for medicinal products (Official Journal C 229, 22/7/1998 p. 4 - 17).		
Note for guidance on minimising the risk of transmitting animal spongiform encephalopathyagents via human and veterinary medicinal products (EMEA/410/01 Rev. 2 ó October 2003) adopted by the Committee for Proprietary Medicinal Products (CPMP) and by the Committee for Veterinary		

EU Legislation	Relevant Articles	Explanation/Comments from stakeholders
Medicinal products (CVMP) (Official Journal C 24, 2006 p. 6 - 18).		
Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (Official Journal C 243/1, 2008).		