Project Group on facilitating supply in small markets

Position Paper and Recommendations[1]

1 Executive Summary

This position paper has been developed within the platform on Access to Medicines in Europe as one of the work areas of the Process on Corporate Responsibility in the Field of Pharmaceuticals and under the Project Group on Facilitating Supply in Small Markets. Countries (Cyprus, Estonia, Iceland, Latvia, Lithuania, Malta and Slovenia, in the following text referred to as SM domain) and economic operators in this project group exchanged their experiences and opinions throughout the process.

The main purpose of this project was to identify some of the problems common to small markets and gather proposed solutions and recommendations from all the parties involved.

To achieve this purpose various activities were performed, including: the presentation of national experiences by participating countries; a mapping exercise to obtain an overview on problems related to unavailability; the exchange of views with economic operators; a review of the application of international experiences on regional pool procurement; and the Baltic pack project to facilitate the circulation of a common pack in the Baltic States.

Several enquiries were prepared to document which medicinal products commonly had problems related to unavailability or supply shortages. Countries and economic operators were contacted to gather information regarding the main problems related to the supply of medicinal products. From the countries' perspective, the main problems cited were: lack of marketing authorisation, shortages of supply, no effective availability, unaffordable prices and marketing delays. Economic operators cited the following key factors: low profitability at allowed prices/margins, local language requirements, price spillovers through international reference pricing, and/or risk of parallel trade. A mapping exercise based on selected products was also prepared to demonstrate the existence of relevant supply problems.

Access and affordability are closely interrelated. In this sense, it is difficult to differentiate among availability problems attributable to a market's small size and those problems that are caused by low income and/or financial constraints. This is particularly relevant in the SM domain since six of the seven countries have an average Gross Domestic Product (GDP) per capita below the EU average. The idea of differentiated pricing could be further explored taking into account the internal market provisions of parallel trade.

Regional cooperation can be a mechanism to alleviate issues of unavailability. Experience acquired through the "Baltic pack project" (one multilingual package concerning the labelling for all three Baltic Member States) enabled them to produce larger batches, decrease administrative costs and increase the availability of medicines. Several other international

[1] The present document is without prejudice to any existing or future EU/ national and international legislation.

experiences outside the EU were reviewed, but substantial structural and practical differences were noted in relation to the existing EU system thereby limiting their application. .

Some recommendations that emerged from discussions between the different stakeholders included: the establishment of a shared information platform for supply problems would be a valuable tool because the information obtained could then provide a basis for facilitating further discussions regarding possible practical solutions; shared information on needs/quantities/products on the supply-demand level to address the possibility of common purchasing initiatives that encompass specific products of public health interest (e.g. specialised products, orphan medicinal products, certain vaccines, other medicinal products of common interest, etc); the implementation of national provisions and practical solutions to improve access to medicines, such as the "Cyprus Clause"; import licensing and/or multilingual packs; the incorporation of references on specific legislative strategies and practices that have proven useful in solving supply problems, for example, Articles 5 and 126a from Directive 2001/83/EC; addressing specific regulatory tools perceived as barriers to product availability, for example, adapting regulatory costs and fees or packaging requirements; including introduction of provisions for public service obligation in national legislation; cooperation with industry to improve access to patient information and to implement transparent and effective criteria to assess methodology.

2 Developing common positions

2.1 Introduction

The positions expressed in this paper have been developed within the platform on Access to Medicines in Europe as one of the work areas of the Process on Corporate Responsibility in the Field of Pharmaceuticals. The platform was dedicated to enhancing collaboration among Member States and all relevant stakeholders in order to find common, non-regulatory approaches to timely and equitable access to medicines. The Terms of Reference and the composition of the Platform are provided in Annex I to this document.

One of the platform's concrete initiatives is the Project Group on Facilitating Supply in Small Markets which, along with all the other groups operating under this platform, is co-chaired by DG ENTR and a volunteer country. In the case of this group, the co-chairing country was Slovenia. The participation of all stakeholders in the Process on Corporate Responsibility in the Field of Pharmaceuticals was voluntary. DG ENTR facilitated the procedure by assuming the role of secretariat, organising meetings and inviting all interested members of the Platform (competent authorities and other involved stakeholders) to nominate their representatives if they wished to participate in the meetings.

The Project Group on Facilitating Supply in Small Markets focused on access problems faced by smaller Member States, as defined in the Terms of Reference. These markets tend to suffer from systematic and documented unavailability or insufficient supplies of some medicinal products.

Participants in this project group identified small markets in EU and EAA countries that were facing problems regarding the availability of certain medicinal products and that could result in public health risks. They identified the following countries for their review: Cyprus, Estonia, Iceland, Latvia, Lithuania, Malta and Slovenia (in the following text referred to as "SM domain"). Other countries, regardless of their size, could participate in the project provided they met the criteria of markets with supply problems or could provide evidence of possible solutions and best practices.

According to EU primary legislation, Member States are responsible for organizing their own health insurance systems as well as for allocating resources dedicated to healthcare; therefore, decisions regarding pricing and reimbursement of medicines are decided on a national level. Experience has revealed the existence of several economic thresholds which limit availability and make it difficult for economic operators to ensure sustainable delivery of medicines in small national markets. On the one hand, medicinal products are important to safeguard public health but on the other hand, the economic viability of participating stakeholders must also be taken into consideration.

The project's aim was to facilitate increased access to medicines in small markets without negatively impacting innovation or patients' overall access. More specifically, the project group acknowledged that the impact of short-term solutions should not create spill over effects on other markets (via mechanisms such as international reference pricing or principles

such as free movement of goods). For this reason, it was determined that availability issues not specifically related to small markets would be considered outside the scope of their work (e.g., general affordability issues unrelated to market size).

Given the multi-faceted nature of issues affecting each small market, this project placed a special emphasis on identifying some of the problems common to small markets that hamper the promotion of sustainable availability and delivery of medicines. Participants worked within the context of a non-regulatory approach and proposed possible common solutions or recommendations for all concerned parties.

Useful information was exchanged among participants, and programmed enquiries and studies were performed to gather and analyse data on typical supply problems in the SM domain.

2.2 Activities of the group

In the context of information exchange, the following activities took place:

- All participating countries presented their national experiences and stated that they suffered from systematic and documented unavailability or shortages in the supply of certain medicinal products. . The UK's Pharmaceutical Services Negotiating Committee (PSNC) was cited as a good example of a publicly accessible data base. The objective was to examine whether positive outcomes could be obtained by publicly documenting and continuously updating information regarding the non-availability of medicinal products.

- With help from EMINET[2], the group agreed to undertake a mapping exercise designed to create an overview of problems affecting the non-availability of products in the participating countries. All of the group members provided information to enhance the data search

- Economic operators active in small markets were given an opportunity to present their ideas on the relationship between issues of availability and affordability. This exchange of views further enriched the project group's work. Economic operators focused particularly on the possible connections between each country's GDP per capita and the effects of using a reference pricing system.

- EMINET supported an effort to examine the application of international experiences on regional pool procurement and the possibility of implementing them in small markets under the currently existing legal framework.

[2] The EMINet project – European Medicines Information Network on Pricing and Reimbursement of pharmaceuticals – was launched in December 2008 and is co-funded by the European Commission (DG Enterprise and Industry). It aims to support EU Member States, EEA-EFTA countries and the Commission by providing information, technical expertise and analysis on pharmaceutical pricing and reimbursement policies and related topics.
EMINet is established by three partners:

1. Gesundheit Österreich GmbH, Österreichisches Bundesinstitut für Gesundheitswesen -GÖG/ÖBIG- located in Vienna/Austria (acting as Leader)
2. Andalusian School of Public Health, Escuela Andaluza de Salud Pública, -EASP- located in Granada/Spain
3. LSE Health and Social Care (LSEHSC) - a research centre in the Department of Social Policy at the London School of Economics and Political Science - located in London/United Kingdom

- A pilot project was launched in the three participating Baltic States to investigate how to better facilitate the circulation of a common pack (Baltic pack), based on the traditional cooperation of these markets.

2.3 Findings of EMINET enquiries

The group prepared questionnaires to document the types of medicinal products that were either unavailable or in short supply. The methodology used for gathering information, as well as the results of the mapping exercise, can be found in Annex II.

The goal of the mapping exercise was to identify how cooperation could be improved and to examine the possibility of special incentives for economic operators, thus contributing to an overall improvement in supply. EMINET provided support in this area by contacting countries and economic operators (in coordination with national and international associations) to map their views regarding the supply of medicinal products in small markets and identify possible local factors which influence the problem. From the countries' perspective, the main problems cited were: non-registration, shortages of supply, no effective availability, unaffordable prices and marketing delays. From the economic operators' perspective, answers were received from innovator companies, generic manufacturers, and pharmaceutical full-line wholesalers. Several problems were identified, the main ones being: low profitability at allowed prices/margins, local language requirements, price spillovers through international reference pricing and/or risk of parallel trade.
The scope and methodology of this analysis focused on the varying nature of supply and access issues in each small market, attempting to detect the confluence potentials of the demand and supply sides of these markets.

2.4 Necessity for a holistic approach; legal status, regulatory requirements vs. pricing implications

While the project group's focus was on non-regulatory approaches, special consideration was given to the areas in which existing regulatory provisions could be perceived as adversely influencing the ability of economic operators, state authorities, and other stakeholders in the SM domain to ensure a continuous supply of pharmaceuticals.

Decisions by economic operators to bring a medicinal product on to the market are always driven and influenced by a combination of factors (regulatory, legal and commercial). Thus, a holistic approach must be used to find solutions aimed at increasing availability. Eliminating one barrier will not significantly change the situation or lead to any satisfactory improvements in availability.

Valid marketing authorisations exist across all EU for centrally authorised products, assuring legal status for these products in every Member State. Still, they are not always launched in some national markets of the SM domain. Moreover, Member States of the SM domain are often not included in DCP/MRP procedures, or even if they are, the launch of the product is sometimes delayed or outstanding.

Marketing Authorisation Holders (MAH) would benefit by holistic incentives to actively apply for the Marketing Authorisation and to market their products in each particular Member State. At the same time, patients in those markets would benefit from the presence of these products as well.

In addition to the findings of the Report of Task Force HMA (2007) - Availability of Human Medicinal Products[3][4] - EMINET conducted a survey with competent authorities to identify specific shortages in these markets.

Member States with small markets face significant problems in terms of medicine availability, particularly with low volume, low price and specialised products intended to treat severe and/ or rare diseases. Availability of medicines in smaller markets appears to be essentially influenced by regulatory requirements which, when combined with economic considerations, affect both the innovative and generic segments of the market.

2.5 Interrelation of Access and Affordability

When lack of availability is conditioned by economic forces it is difficult to ascertain which problems are attributable to small market size and which are caused by low income and/or financial constraints. This is particularly true in the SM domain, where six of the seven countries have an average per capita Gross Domestic Product (GDP) below the EU average.

Benchmarking reports on availability and uptake of medicines show significant variations in uptake of medicines across EU countries. These variations appear to be linked to differences in the average GDP per capita.

The 6 December 2010 Council conclusions on innovation and solidarity in pharmaceuticals call upon Member States to "examine, based on the principles of solidarity, economically viable and efficient approaches to facilitate availability and access to valuable innovative medicinal products throughout the EU, while respecting the principle of subsidiarity and the competences of Member States, e.g. on affordability and sustainability of health systems". This requires Member States to set clear and common expectations on what innovation they consider valuable and would reward through the establishment of value-based pricing systems.

2.6 Possible improvement of regional cooperation regarding multilingual labelling– examples of Baltic States

Building on current and historical cooperation among the Baltic States, GIRP— in collaboration with EFPIA, EGA and EUROPABIO - also designed a parallel project to address the feasibility of the free circulation of specifically developed multilingual packs in three Baltic Member States (EE, LT, and LV). Due to the fact that all three of these markets are small, marketing authorisation holders (MAHs) frequently use Baltic packages to sell the same package throughout all three Baltic Member States, thus enabling them to produce

[3] http://www.hma.eu/fileadmin/dateien/HMA_joint/02-_HMA_Topics/05- Availability_Medicines/2007_11_ReportTF.pdf
[4] http://www.hma.eu

larger batches decrease administrative costs and increase the availability of medicines. The same principles could be applied to bilingual country packs, which could then be marketed without any changes in two of the three Baltic Member States. Currently, once each Member State has granted its authorization, medicinal products in Baltic packages can freely circulate among all three countries. The degree of administrative requirements, however, can vary in complexity from state to state. Since the same legislative framework applies in all three states, in-depth discussions were conducted to examine whether requirements and practices affecting the regulation of relevant medicinal products and economic operations could be streamlined to increase the common pack's circulation. Further measures were also examined to identify and reduce existing differences in the countries' administrative procedures within their existing legal frameworks. Member State representatives also emphasized that under no circumstances would they accept any solutions that could lead to an unwanted depletion of products in the national exportation market. If the participating countries and economic operators choose to proceed further with their cooperation, discussions concerning the common Baltic pack are likely to extend beyond the remit of this group, but the approach could prove to be useful for other combinations of Member States.

Eminet provided key information to promote an idea for possible regional cooperation in alleviating issues related to unavailability by examining the possibility of applying an approach based on regional pool procurement between small markets. That information highlighted several international experiences from non-European regions whose characteristics differed from than those in the SM domain. The data revealed the existence of substantial obstacles in the possible application of such cooperation, particularly under the current legislative framework.

2.7 Establish coherence with other groups operating under the Platform on Access to Medicines in Europe

To be consistent with work done by other project groups participating in the Platform on Access to Medicines in Europe, this group strove to weigh the implications their proposals could have on the small market environment. It maintained contacts with other projects working under the same platform, addressing the feasibility of their solutions and deliverables in the small market environment.

2.7.1 Assure Access to Biosimilars

Biosimilars are in practice approved centrally and the product packaging must be translated into all EU languages. A proportional penetration of biosimilars in therapeutics should be expected for the SM domain. Mobilization of pharmacists in providing patient information for low-volume biosimilar products can be relevant.

As in larger markets, patients in small markets should discuss the benefits and risks of treatments based on biological and/or biosimilar medicines with their physician, taking into account that a biosimilar medicine is developed to be highly similar to its reference medicine in terms of quality, safety and efficacy.

A biosimilar and its reference medicine are expected to have the same safety and efficacy profile and are generally used to treat the same conditions.

2.7.2 Develop managed entry agreements on national and cross-border basis

An increasing number of countries consider Managed Entry Agreements (MEA) to be a valuable strategy in balancing access to medicines and increased costs, particularly when levels of uncertainty can prevent or delay the uptake of new and expensive technologies. Under certain specific conditions, these agreements can facilitate access to a health technology subject to specified conditions through a variety of mechanisms that address issues such as uncertainty about the performance of technologies, managing the incorporation of technologies in ways that maximize their effectiveness, or how to limit their budget impact.

Results from the working group's systematic analysis showed that Member States with small markets had limited or no engagement in MEA. One explanation for this is that such states lack the negotiation power to succeed in that area. This scenario can cause delays, threaten exclusion from positive lists and / or contribute to significant price dispersion among EU countries. In the end, Member States with "small budgets" bear the burden through unacceptable levels of financial risk.

The working group proposes strengthening the cooperation between Member States capable of successfully engaging in MEA and small market states lacking that capacity. Such an agreement would enable the latter to participate in contractual agreements (a bilateral or multilateral collaborative approach). Clearly, for this to occur, economic operators (pharma business) must also be in agreement.

2.7.3 Develop mechanisms of coordinated access to Orphan Medicinal Products (OMPs)

Most OMPs result from applying modern biotechnology in the development and/or manufacturing process. Because many of these medicinal products are used to treat rare diseases, manufacturers can only recoup their development costs through sales to a limited number of patients worldwide. Consequently, acquisition costs per patient are higher. Unlike in clinical trials conducted for more common diseases, manufacturers of biological drugs face significant difficulties in recruiting a sufficient number of patients into their clinical trials. This often leads to weaker clinical evidence and increased scepticism about their reliability, which impacts negatively on access to OMPs.

The small market group considers differential pricing to be a feasible option which could be considered as applicable for OMPs and applied to small markets.

2.7.4 Good Governance for non – prescription drugs (OTC)

Non-prescription medicines, also known as Over the Counter (OTC) medicines, are available without a prescription and play an important role in empowering people to take decisions about their health. OTC medicines also offer economic benefits in healthcare and contribute to the pharmaceutical sector's economic performance. Since Member States' policies differ considerably when it comes to classifying medicines as prescription or non-prescription, the group is working on identifying best practices to facilitate access to these products to ensure the maximum protection of public health, as well as informed use and choice. Within its remit the group considered the perspective of all players, including small markets. Member States of the SM domain could benefit from dedicated mutual information-sharing on their OTC switching decisions. This could decrease the sometimes fragmented legal status of certain products in the national markets of the SM domain that some believe represents an additional administrative or economic burden that deters suppliers from authorizing and marketing such products.

3 Recommendations

3.1 General note:

The project group's debate on availability in the small markets revealed the complexity of the issue, often influenced by country-specific variables or conditions. Members agreed that the overall objective is to safeguard public health irrespective of market size and ensure patients' timely access to medicines.

The recommendations – which address issues specific to small-markets - only apply to the countries recognized in this Project as EU/EEA small markets, i.e. the SM domain. The project group's intention was to draft recommendations that would be consistent with existing EU and national regulations. Group members acknowledged that some of their recommendations might face difficulties in implementation in some Member States.
All of the following can be valuable tools for any future actions on the EU level.

Overcoming the problem of access to medicinal products which are clearly in the public health interest but whose economic viability is insufficient for suppliers requires tackling the problem with instruments capable of providing continuous, and at least mid-term, solutions. These could include information-sharing and capacity building through increased co-operation among competent authorities and interested stakeholders. Once evidence on the causes of such shortages has been documented, and if there is also sufficient evidence that an adverse relationship between economic incentives and supply exists, then potential solutions can be identified to improve access to medicines.

The members of the group endorsed the idea of organising regular meetings that could be hosted by the Commission services in order to monitor the situation in small markets. The exact intervals between meetings are to be determined.

3.2 Recommendation 1 - Establishment of a shared information platform for supply problems in the SM domain or beyond

To facilitate supply in small markets participants are encouraged to share with others the positive or effective measures they have implemented to improve supply in small markets.
The objective is to ensure the continuous and public availability of information on possible deficiencies without compromising issues related to commercial confidentiality. This area includes a wide range of possible information, for example, lists of unavailable medicines identified by: active substance, (international non-proprietary name INN), pharmaceutical form, strength and other relevant information such as trade name or indication, work sharing, best use of existing regulatory enablers[5] or others.

[5] E.g. the use of multi-language packs, stickers or packs allowed in other countries with common language, where enabled by national legislation

Competent authorities are encouraged to be proactive in publishing information on products systematically missing from their market. The group endorses the idea that such an updated list would be a valuable tool and that this information could provide a basis to facilitate discussions for possible practical solutions. The possibility of future meetings based on the above mentioned structure merits further exploration.

This recommendation could result in the preparation and maintenance of a list that reflects problems in supply/ and/or access in small markets, based on the general description INN name, ATC5 code, pharmaceutical form and strength. Such an instrument could acquire broader importance because some larger EU Member States also face supply problems.

Some group members (for example Slovenia) stated that they had already developed a data base to list medicines lacking in their market and which, according to their criteria, could cause problems to their healthcare system.

Discussions were held on how to obtain a better overview of the systematic and documented unavailability or supply shortages of some medicinal products. The idea of using a common portal was examined. An already existing portal could be used (for example, at the level of HMA or one of the national agencies of the SM domain) with links to the portals developed in the affected small markets. Inclusion and exclusion criteria for product listings need to be elaborated. Certain technical aspects of this possibility would also require further examination, including the possibility of connecting already existing national solutions. Regular periodic meetings between authorities and stakeholders from Member States would assure the information's quality and relevance.

Information on the systematic reasons behind unavailability or shortages of supply by the competent authorities in disease areas with specific examples of products was collected and exchanged, focusing on special therapeutic areas.

EMINET supported this activity by developing a draft template for the competent authorities of the SM domain and the relevant stakeholders, in order to facilitate the exchange of information and to help mapping of the problem in supply as listed in the Annex II.

3.3 Recommendation 2 - Shared information on needs/quantities/products on supply-demand level

The group addressed interest and feasibility for a common coordinated purchasing initiative encompassing specific products of public health interest (e.g. specialised products, orphan medicinal products, some vaccines, other medicinal products of common interest, etc). In addition, for a broader group of products which do not exist everywhere, particularly in small markets, more indirect ways could be considered for national purchasing, resulting in higher capacity and increased predictability both in terms of supply and demand.

An assessment could be done on existing practical solutions to improve access to medicines, such as innovative contracting approaches or cross border co-operation as currently enabled/disabled by national laws. Improved co-operation in identifying and analysing national/regional/international experiences of purchasing initiatives could enhance access to medicines throughout the SM domain.

Contracting with multiple stakeholders whose public health objectives and financial priorities often differ is inherently more complex and can be exceedingly difficult. Some pharmaceutical companies have a long experience with national and international public tendering systems such as UNICEF or PAHO (Pan American Health Organisation) and early and sustained dialogue with industry should be encouraged when designing cross-border joint procurement systems. Issues to be addressed include:

- Who will be the customer? Individual recipient countries?
- Will there be a single tender and product specification, issued, negotiated, adjudicated and managed by a single authority?
- Will there be a series of national tenders sharing some common terms, but with local variations in specification, local negotiation, adjudication and management taking into consideration that various Member States may have slightly different public health priorities?
- Who manages logistics from the customer side? Member States?

. An evaluation should be done to learn whether it is feasible to tighten provisions in this area to ensure as harmonised an approach as possible. The group anticipates that this task may be achieved by new EU public procurement legislation currently under development.

As a general rule, cross border joint procurement should not compromise good clinical decision-making on what is best for individual patients in the different member states. Both healthcare provider and patient must be able to make the best possible treatment decisions for a particular condition.

3.4 Recommendation 3 - Implementation of national provisions (e.g. »Cyprus Clause«, Import Licensing, MS specificities, multilingual packs) - Policies and practical solutions to improve access to medicines

Once a full understanding of the different supply issues for each country in this policy area has been obtained it would be worthwhile to explore experiences from workable solutions to improve patient access to medicines in the SM domain, such as innovative contracting approaches or the application of other cross-border measures to facilitate the supply of medicines. Every country, regardless of its size, is influenced by different parameters. Reasons for the problem of unavailability of medicines are not always the same.

Information-sharing included data on the effects of particular provisions and working experience on legislative and regulatory practices as well as or other solutions aimed towards achieving stable and predictable medicine supplies.

Although it was not the aim of this group to discuss regulatory issues or analyse the existing legal framework, some regulatory aspects related to the implementation of Directive 2001/83/EC were mentioned as well. The group referred to DG SANCO’s on-going study on the Availability of Medicinal Products which concerns all EU/EAA countries and will continue to examine issues of availability as they relate to existing EU legislation.

3.5 Recommendation 4 - References on specific legislation – Directive 2001/83/EC6 -, strategies and practices that have been useful in solving supply problems and that might be applied in other SM domains

3.5.1 Article 126a

In the absence of a marketing authorisation or of a pending application for a medicinal product authorised in another Member State, the licensing authority of a SM domain may authorise, for justified public health reasons the placing of that medicinal product on the market in a SM domain, provided that the said product is authorised in another Member State (EU/EEA country). This authorisation is in line with article 126(a) of Directive 2001/83/EC. This authorisation procedure is being applied mainly to cover the public health need created by the lack of applications for marketing authorisation. For example in Malta since the first issue of authorisation by article 126(a) in October 2006 there was a substantial increase in the number of applications and authorisations under this procedure. By October 2012 out of a total of 4178 medicinal products registered in Malta, 1540 medicinal products had been authorised under this procedure.

It is important to emphasize that authorisation by article 126a should in no way be considered as a way of circumventing the current procedures stipulated by the EU legislation. However, the group considered that the only systemic solution which safeguards public health appropriately is the one that includes the SM domain within the concerned Member States of the MRP and DCP procedures[7] (regulatory procedures for obtaining a market authorisation: Mutual Recognition and Decentralised).,

3.5.2 Article 5

Another part of the regulatory framework is article 5 of Directive 2001/83/EC which stipulates that a Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients on his direct personal responsibility.
The particular national legislation of a SM domain Member State based on Article 5 of the Directive 2001/83/EC may provide for an alternative legal status of a product granted in exceptional cases and under specific terms to a medicinal product without a local marketing authorisation in order to safeguard public health.

3.6 Recommendation 5 - Qualification of specific regulatory tools identified as a barrier to availability of the product on the market and assessment of possibilities to decrease their impact

Regarding a holistic approach to the SM domain supply problems, the project group identified, albeit beyond its initial scope, some regulatory issues that deserve attention in possible future statutory development. . The group fully acknowledged that within the

[6] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0128:en:PDF
[7] http://www.hma.eu/91.html

existing Acquis, the degree to which procedures can be adapted is limited to the level of technical interpretation and streamlining of certain national provisions and practices.

However, it was acknowledged that certain regulatory elements influence the MAH's decision to apply for MA and for enter markets in the SM domain, such as:

- High regulatory costs
- Regulatory requirements applicable to packaging for multilingual packs
- Regulatory procedures do not always permit quick responses that would better accommodate the needs of markets or patients.
- Some problems have been noted in relation to the addition of another MS (e.g. member states of the SM domain) during on-going DCP procedures. In addition, even in those cases where the Marketing Authorisation Holder is willing to extend the existing Marketing Authorisation to another (small) MS, the workload required for a Reference Member State (RMS) to update the initial assessment report, as well as a company's investment in updating the relevant dossier, may be disproportionate and possibly without commercial benefit due to high regulatory costs and the product's low price/low volume.

With regard to labelling, the applicants have experienced that it is not always practical to add a sticker on a pack coming from another MS (different language). In some Member States formal variations (including fees) have to be submitted, while in others an authorisation for the application of sticker is granted without a formal marketing authorization variation procedure.

3.6.1 Recommendation 5.1 – Dealing with specific regulatory provisions

With regard to the existing regulatory framework – Chapter 4: Mutual Recognition of Authorisations of Directive 2001/83/EC - the project group recommends that the competent authorities reflect further on whether they could also implement some of the pragmatic practices already used by some of the small markets. An example is the so called "zero-day MRP" already used by some of the smaller Member States. The group considers it necessary for the Commission to address this concept, which was presented in the HMA group.

Luxembourg, despite being a small market, undoubtedly benefits from its multi-language environment. It doesn't face the kinds of problems that other small markets examined by this group had to confront, therefore, its practices could be further explored in terms of horizontal legislative solutions. Such approach could facilitate the uptake of products, for example by applying the recognition of other EU official languages for product labelling, which are concurrently one of the official languages of the concerned Member State[8].

The Baltic Pack can be viewed as an effort to create one bigger market rather than three smaller ones.

Consider whether co-marketing might be one way to address the issue of unavailability in small markets with regard to medicines that have been granted a marketing

[8] Article 63(3) of Directive 2001/83/EC gives the possibility for exemption from language requirements for reasons related to availability.

authorisation through the centralised procedure. This should be done in compliance with the applicable provisions of Regulation 726/2004 and the related guidelines.

The specific needs of small markets should be adequately reflected in the regulatory framework, with regard to its application.

3.6.2 Recommendation 5.2 - Explore the possibilities for adapting the regulatory costs and fees

Competent authorities should consider lower fees/fee waivers for products identified as missing on their market, not only for initial submission fees but also maintenance fees. The same approach could be extended to the fees for other administrative processes that determine the national uptake of a medicinal product: health technology assessment procedures as well as pricing and reimbursement procedures.

3.6.3 Recommendation 5.3 - Adaptation of packaging requirements

The specific provisions for packaging are regulated by Directive 2001/83/EC (Title V – Labelling and Package Leaflet).

The possibility of using a multilingual pack/another language pack is a key factor in facilitating the circulation of a medicinal product in a small market. The project group recommends a more pragmatic approach in the procedures that affect labelling, such as the specific technical requirements for minimal font size used for multilingual packs, in line with readability requirements in the legislation Similarly, experiences could be shared among Member State authorities who have decided to use stickers on foreign language labelled packs without requiring the submission of formal variation applications in all concerned Member States.

3.6.4 Recommendation 5.4 - Member States could include provisions for public service obligation in national legislation

Directive 2001/83/EC - Recital 38 and Article 81 both refer to the public service obligation in terms of the continuation of supply of medicinal products. . It is recommended that MS place these obligations on wholesalers and pharmacies active on their territory, in compliance with this Directive and in compliance with their pharmacy legislation respectively.

3.6.5 Recommendation 5.5 - Member States could implement multilingual labelling solutions with certain supply safeguards

The project group examined the possible streamlining of administrative requirements among the three Baltic Member States with regard to the authorisation of medicinal products that are presented in multilingual Baltic Packs and are intended for sale in those countries – provided such products have an appropriate multilingual packaging, a leaflet, and a valid Marketing Authorisation in each of the three Baltic countries.
Those products that have already been granted legal status in another Baltic Member State should be ensured maximum flexibility for their circulation.
The project group proposes that competent authorities exercise maximum flexibility in setting requirements applicable to both medicinal products and economic operators

involved in this type of distribution, while at the same time supporting any measure of the exporting country to maintain uninterrupted and continuous supply in its national market. In that respect, Baltic packs should circulate freely amongst the countries in which they have legal status, but exports should not be done in a way that could endanger the availability of medicines in the exporting country.

Based on the experience gathered in the Baltic Pack case, a similar approach using a multilingual package and leaflet is recommended for other MS as well.

3.7 Recommendation 6 - Specific non-regulatory tools for cooperation with stakeholders: Economic operators and small size markets relations

Stable economic operations are important in ensuring continuous supply but the functional presence of certain actors, such as full line wholesalers, is not always guaranteed in all countries. The role of wholesalers in mitigating problems of availability in small markets should be further explored.

A survey on economic operators showed that they could improve the delivery of these products to more than one single small market and contribute to mitigating shortages of certain products.

The survey examined special incentives to economic operators. Experience on existing statutory solutions and best practices implemented by the particular Member States were shared in this project. Principal factors influencing the trade of these products were addressed with the aim of decreasing risks that affect both the demand and supply side of the markets.

3.8 Recommendation 7 - Cooperation with industry: strategic development of the value of medicinal products and pricing regulation models

To ensure more effective supplies in small markets the project group explored ways to improve co-operation through information-sharing, general ethical principles influencing the accessibility of medicinal products on both the demand and supply side, and other approaches aimed at providing better incentives for manufacturers to enter into direct supply agreements with purchasers of pharmaceuticals in particular Member States or clusters of Member States.

Issues of availability and affordability in the current reference price system were further elaborated, as well as negative implications for patient access in the more economically vulnerable (lower GDP per capita) Member States.

The group recommends further exploring the possibility of applying a differentiated pricing system, taking into account current differences in socio – economic conditions stemming from the economic crisis and on-going fiscal restructuring programmes in some countries. Clearly such considerations should examine the incompatibilities of approaches such as external price differences and internal market provisions of parallel trade.

3.9 Recommendation 8 - Improving access to Patient Information

The group recommends that competent authorities engage in dialogues with pharmacists' associations to improve access to the low-volume medicinal products that have centralized marketing authorization. These products often reach the SM domain with labels printed in other languages. In such cases, local pharmacists could, upon request and upon exemption provision by national competent authority, provide support to the users of medicines by promptly providing them with printouts of Patient Information Leaflets and a Summary of Products Characteristics or provide them in a more user- friendly manner, for example by giving them links to websites that post official information at the EU- or MS–level.

3.10 Recommendation 9 - Implement Transparent and Effective Methodology Assessment Criteria

Approaches to improve access to medicines in the SM domain should be assessed within the limits of commercial confidentiality and in compliance with EU competition law regarding their potential impact on specific small market healthcare and economic environments, as well as risks for causing unintended consequences beyond those limits.

Clear criteria should be used when implementing any measure or initiative. This also applies to any further action on the EU level to assess proposed solutions, and should include the following:

- Proportionality of the measure/initiative
- Effectiveness of the measure/initiative
- Overall impact on the healthcare system of the relevant small markets
- Ease of implementation
- Compliance with current acquis

4 Annex I Terms of Reference

4.1 Introduction

The platform on Access to Medicines in Europe is one of the work areas of the Process on Corporate Responsibility in the Field of Pharmaceuticals. The platform is dedicated to enhancing collaboration among Member States and all relevant stakeholders, in order to find common, non-regulatory approaches to timely and equitable access to medicines.

Within the platform, one of the concrete initiatives is the Project Group on facilitating supply in small markets which suffer from systematic and documented unavailability or shortage of supply of some medicinal products.

The problem of deficiencies of medicinal products in small markets has been underlined in the past by the working group on Pricing of the Pharmaceutical Forum9, by the relevant report of the Task Force of Heads of Medicines Agencies (from a regulatory perspective)10 and by the Commission Communication "Safe, Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector"11. This project group is to be in consistency

[9] http://ec.europa.eu/pharmaforum/docs/pricing_medicines_en.pdf
[10] http://www.hma.eu/uploads/media/Availability_medicines_HMAMG_TF_Report.pdf
[11] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0666:FIN:en:PDF

with other activities as a holistic approach is necessary to create efficient incentives to facilitate supply in small markets.

For the purpose of this project, small markets (among EU and EAA countries) which are facing problems in terms of sufficient availability of some medicinal products and that could result in risks of public health are the following: Cyprus, Estonia, Iceland, Latvia, Lithuania, Malta and Slovenia. This does not exclude participation to the project or exchange of ideas with other interested countries irrespective of their size provided it meets the criteria of markets with supply problems, or to provide evidence of possible solutions and best practices.

Taking into consideration the varying nature of issues affecting each small market, the aim of this project is in particular, to identify some of the common problems which have been noted in the small markets and create obstacles in the promotion of sustainable availability and delivery of medicines in the context of a non-regulatory approach and propose some possible common solutions or recommendations, with the participation of all concerned parties.

It should be ensured that the other four projects of the Platform on Access to Medicines in Europe, would take into account the implications of their proposals to the small markets environment. This project group should be connected – possibly through a system of rapporteurs – with the other four ongoing projects of the platform, addressing inter alia the feasibility of their solutions and deliverables in the small markets environments.

The recommendations - addressing small-market specific issues - would only apply in principle to the countries recognized in this Project as EU/EEA small markets. At the same time, the aim is to facilitate increased access to small markets but without unintended consequences on the valorization of innovation and patients' access overall; in particular the Project Group's recommendations should acknowledge that the impact of short-term solutions do not create spill over effects on other markets (such as international reference pricing or free movement of goods). For this reason, it should be ensured that availability issues not specific to small-markets – like general affordability issues that are not due to small market size – will be considered out of the scope of the project group.

4.2 Scope and objectives

According to the Treaty Member States are responsible for the organization of their own health insurance systems as well as for the allocation of resources dedicated to healthcare, therefore decisions regarding pricing and reimbursement of medicines are decided on a national level. Experience has shown the existence of several thresholds of economic nature which limit availability and create difficulties for economic operators in order to ensure sustainable delivery of medicines in small national markets. On one hand medicinal products are important to safeguard public health and on the other hand economic viability of involved stakeholders should be established. The Project Group will make sure that any recommendations are fully consistent with existing EU and national regulations.

For medicinal products which present clear public health interest and at the same time insufficient economic viability for suppliers, ways of overcoming the problem of access should be tackled with instruments that would provide continuous and at least mid-term solutions. These could be information sharing and capacity building by increased co-operation of competent authorities and interested stakeholders. Identification of potential solutions

should take place once documented evidence of the causes of such shortages has been established and if there is additionally sufficient evidence that there is an adverse relationship between economic incentives and supply, affecting access to medicines.

While the Project Group's focus is on non-regulatory approaches, particular attention should be given to the areas where existing regulatory issues adversely influence the behaviour of economic operators, state authorities and other stakeholders in small size markets in terms of ensuring a continuous supply of pharmaceuticals.

4.3 Possible areas of co-operation – possible areas of common interest

Every country irrespective of its size is influenced by different parameters. The reasons for the problem of unavailability of medicines are not always the same. The following items have been identified as common ground, and are deemed essential when addressing the problem:

4.3.1 Information sharing and exchange of best practices

In this work area participants are encouraged to share with others the positive or effective measures they have experienced in order to facilitate supply in small markets. Within the limits of commercial confidentiality, this area could include a wide range of information, for example, lists of products not available, twining, best use of existing regulatory enablers12 or others. It can also include sharing best legislative and regulatory practices; or other solutions which are aimed towards achieving stable and predictable supply of medicines.

4.3.2 Policies and practical solutions to improve access to medicines

In this policy area, after a full understanding of the different supply issues for each country, it would be worthwhile to explore experience from practical solutions to improve patient access to medicines in Cyprus, Estonia, Iceland, Latvia, Lithuania, Malta and Slovenia, such as innovative contracting approaches or applying other measures of a cross-border nature to facilitate the supply of medicines in small markets.

Interest and feasibility for common coordinated purchasing on specific products of public health interest (e.g. specialized products, orphan medicinal products, some vaccines, other medicinal products of common interest, etc) could be addressed in the group. In addition, for a broader group of products which do not exist everywhere, particularly in small markets, more indirect ways could be considered for national purchasing, resulting in higher capacity and increased predictability both in terms of supply and demand.

Within the limits of commercial confidentiality and in compliance with EU competition law, the different approaches will be assessed with regards to their potential impact on specific small market healthcare and economic environments as well as their risk for acting as causes of unintended consequences beyond this limitation.

[12] E.g. the use of multi-language packs, stickers or packs allowed in other countries with common language, where enabled by national legislation

4.3.3 Economic operators and small size markets relations

Stable economic operations are important in ensuring continuous supply. It has been noted that the functional presence of some actors, like full line wholesalers is not always guaranteed in all countries.

A survey of economic operators who specialize in certain line of products and could bring these products to more than a single small market, could contribute to the mitigation of the shortages for certain products. A work exercise could examine the possibility of supply from a wholesaler in one country to the countries where there are no interested full line wholesalers.

The survey will inter alia examine special incentives to economic operators. Experience on existing statutory solutions and best practices implemented by the particular Member States will be shared in this project. Principal factors influencing the trade of these products should be looked at in order to decrease the risks occurring in both demand and supply side of the markets.

4.3.4 Co-operation with industry

The Project Group will explore ways of better co-operation in order to be more effective with the supply in small markets on the basis of an ethical code, information sharing or other approaches that could provide a better incentive for manufacturers to enter into direct supply agreements with purchasers of pharmaceuticals in particular Member States or clusters of Member States.

4.4 Proposed Work Plan

4.4.1 Information sharing and exchange of best practices

Information on the systematic reasons that cause unavailability or shortages of supply by the competent authorities in disease areas with specific examples of products could be collected and exchanged focusing on special therapeutic areas.

This could result in the preparation and maintenance of a list with problems in supply/ and / or access in small markets, using the general description INN name, ATC5 code, pharmaceutical strength and form.

Eminet13 will support this activity by developing a draft template for the competent authorities of the small markets and the relevant stakeholders, in order to facilitate the exchange of information and to help mapping of the problem in supply. The proposed template will be discussed and agreed by the Project Group participants with Eminet. All this information could lead to a regularly updated list which can be useful for co-ordination and management purposes.

[13] The EMINet project – European Medicines Information Network on Pricing and Reimbursement of pharmaceuticals – was launched in December 2008 and is co-funded by the European Commission (DG Enterprise and Industry). It aims to support EU Member States, EEA-EFTA countries and the Commission by providing information, technical expertise and analysis on pharmaceutical pricing and reimbursement policies and related topics.
EMINet is established by three partners:

4. Gesundheit Österreich GmbH, Österreichisches Bundesinstitut für Gesundheitswesen -GÖG/ÖBIG- located in Vienna/Austria (acting as Leader)
5. Andalusian School of Public Health, Escuela Andaluza de Salud Pública, -EASP- located in Granada/Spain
6. LSE Health and Social Care (LSEHSC) - a research centre in the Department of Social Policy at the London School of Economics and Political Science - located in London/United Kingdom

4.4.2 Practical solutions to improve access to medicines

An assessment of the existing practical solutions to improve access to medicines, such as innovative contracting approaches or cross border co-operation as currently enabled / disabled by national laws could be conducted, by co-operation identifying and analysing national/regional/international experiences of the purchasing initiatives that could enhance the access to medicines. Eminet will explore possible international experiences with the aim to present practical outcomes, positive and negative concrete examples and feedback to the Project Group.
All of the above can be a valuable tool for any future actions on an EU level.

4.4.3 Relation of economic operators and small size markets

Economic operators (in the context of the Project Group on facilitating supply in small markets) include EFPIA, EGA, EUROPABIO, AESGP, PGEU, HOPE and GIRP.
The objective of this analysis will be to identify better ways of co-operation and examine possible special incentives for economic operators resulting in overall improvement of the terms of supply.
Eminet will help in this area, by contacting economic operators in co-ordination with national associations and some of the above mentioned international associations in order to map their views regarding supply of medicinal products in small markets and identify possible local factors which influence the problem.
The scope and methodology of this analysis will take into consideration the varying nature of supply and access issues in each small market, and will aim to detect the confluence potentials of the demand and supply sides of these markets. As such, it will be discussed and agreed by the Project Group participants and Eminet.

4.4.4 Conclusions

After the completion of the work of the group, under a horizontal approach, including the information sharing exercise and the collection of data by Eminet, not excluding any possible factors that affect the systematic reasons that cause unavailability or shortages of supply, the group should be able to analyse the findings and also draw some conclusions applicable to small markets as defined in the introduction of these Terms of Reference.

These conclusions should reflect the variety of situations, as well as potentials for synergism in the different targeted Member States.
It would be ideal to produce some recommendations for possible future policy action synergies, avoiding any negative effects as described in the introduction of these terms of reference.

4.5 Methodology assessment criteria

In order to guide the work and the findings of the project group, clear criteria will be used to assess proposed solutions, which will include the following:
Proportionality of the measure
Effectiveness of the measure
Overall impact on the healthcare system of the relevant small markets
Ease of implementation
Compliance with current acquis

4.6 Work Tools

Survey and exchange of practices for very low price & very low volume products;
Eminet co-operation on the development of a draft template as proposed in section 1 of the Work Plan, the assessment as proposed in section 2, and the analysis as proposed in section 3;
Project Group participants (and Eminet when relevant) teleconferences;
Project Group face-to-face meetings; and
A targeted literature survey with the objective to synthesize existing research on issues related to small markets in the view of macro and microeconomics

5 Members of the Platform on Access to Medicines in Europe

DG Enterprise and Industry is chairing the platform.
The Member States and EFTA countries were invited to nominate representatives from their relevant competent authorities in charge of pricing and reimbursement of pharmaceuticals.
The following stakeholders' organisations were invited to take part:
European Patients Forum – EPF
Bureau Européen des Unions de Consommateurs - BEUC
Standing Committee of European Doctors - CPME
Pharmaceutical Group of the European Union – PGEU
European Hospital and Healthcare Federation - HOPE
Association Internationale de la Mutualité - AIM
European Social Insurance Platform – ESIP
European Federation of Pharmaceutical Industries & Associations - EFPIA
European Generic medicines Association - EGA
European Self-Medication Industry - AESGP
European Association for Bioindustries - EuropaBio
European Association of Full-Line Wholesalers – GIRP
Each of the groups operating under the Platform is co-chaired by DG Enterprise and Industry and a volunteer country.

6 Annex II Mapping Exercise

6.1 Background

One of the project groups of the platform on Access to Medicines in Europe is related to facilitating supply of medicines in Small Market. A number of previous EC documents (Pharmaceutical Forum, for example) have highlighted the problems of availability and affordability of some medicines in small markets/countries. Also, the EMINet team produced a previous document on this topic ("Generics in small market of the EU for low volume medicines"[14])

6.2 Objective

To assess the present situation of supply problems in small European countries.

6.3 Methodology

This mapping exercise has been developed in two phases. The first phase consisted in identifying the list of products which have experienced supply problems[15] in the last three years. The questionnaire was sent on April and answers and clarifications were received until June 2012. Answers were received from 7 countries: Cyprus, Estonia, Iceland, Latvia, Lithuania, Malta and Slovenia. It has been a wide range in the reported number of products for which individual countries have experienced supply problems[16]; the differences might be partly attributed to the lack of an agreed operational definition of "supply problem" and because the data on supply problems are not collected systematically in all countries.

In the second phase a list of products (13) was selected based on the frequency of appearance in the national lists (the 13 product on the final list have been mentioned in, at least, three countries): The products selected have been: Chlorambucil, Acetazolamide, Capreomycin, Desmopressin, Fluorouracilum, Furosemide, Melphalanum, Methotrexate, Metoprolol, Phenobarbital, Thiopentone, Tioguaninum and Valproate. For each product in the list a set of questions were requested, including date of marketing authorization, price, reimbursement stated, alleged causes of the problem, etc. Questionnaires were sent at the end of July and answers were received until end of August (some contacts were made later to clarify answers).

[14] http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/monitoring/index_en.htm

[15] The concept of supply problems has been defined in broad way and including, for example, no registration submitted, no effective marketing, delays in launching new medicines, shortages of supply, high/unaffordable prices, others, etc

[16] Cyprus (260), Estonia (129), Iceland (6), Latvia (17), Lithuania (9), Malta (43) and Slovenia (96).

6.4 Results

The main two reasons that account for supply problems, according to the answers received, are the lack of submission for registration (41%) and supply discontinuation (31%). Other reasons are the transfer of MAH (Market Authorisation Holder) (10%), the withdrawal of the marketing authorisation by MAH (10%), unauthorisation (distributed individual use art. 5.1 Directive 2001/83/ EC)[17] (5%) and marketing authorisation not renewed (3%).

The two main assumed causes for the product not being launched in the country are no profitability for the economic operators (68%) and manufacturing problems (20%).

6.5 Conclusions

The outcomes of this mapping exercise do not consist an exhaustive list of shortages, in the concerned countries although they demonstrate the existence of relevant supply problems in small markets in Europe. In spite of the limitations of the selected sample of products (small number of products, not easily comparable, etc.), the results clearly indicate that the products with supply problems are mainly "old" medicines (with more than 40 years in the European market), relatively cheap (but with high price differences between countries -especially when is compared with a non-small country-) and mainly aimed at small patient populations. Given the small sample used in our survey, it seems not justified to rule out the possibility of shortages of other types and possibly more costly products.

7 Work Tools used in the Project

- Survey and exchange of practices for very low price & very low volume products;
- Eminet co-operation on the development of a draft template as proposed in section 1 of the Work Plan, the assessment as proposed in section 2, and the analysis as proposed in section 3;
- Project Group participants (and Eminet when relevant) teleconferences;
- Project Group face-to-face meetings; and
- A targeted literature survey with the objective to synthesize existing research on issues related to small markets in the view of macro and microeconomics

[17] Art. 5.1 (Directive 2001/83/ EC). A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.