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# **Availability of Human Medicinal Products**

**Report of Task Force of HMA MG**

**2007**

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## **Executive Summary**

The Task Force (TF) on availability of human medicinal products was established by the Heads of Medicines Agencies MG in March 2007. The establishment of the TF was followed by the identification of the problem of unavailability in the sector of human medicinal products, especially in small and medium-size countries.

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Chapter 1 of the Report is presenting the introduction and is describing the background and current situations to the problem.

The market of medicinal products in the European Union is a highly regulated area. Differing from the idea of “New approach”, medicinal products are regulated differently and their entering to the market is not only the responsibility of their manufacturer. The authorisation for placing on the market is granted by the regulatory authorities of the Member State or the European Commission after an assessment by relevant expertise. However, this authorisation can only be issued after the manufacturer has applied for it. This concept works well in an ideal world where the manufacturers are interested to place their products equally to all the markets, but in reality this may not be the case. If such situation happens, we can see that there are not enough instruments for the governments to handle and solve such situations.

The unavailability of some medicinal products poses a real threat to public health and welfare. The lack of authorised medicines poses problems for patients, physicians, consumers and governments. The availability of human medicinal products on small markets is a public health concern and thus requires attention. Since the problem concerns public health, it is necessary to define the problem and to propose actions to be taken in favour of patients.

The main reason for the industry not to put their products on the market in a Member State seems to be the size of the market. Size of the market and national language are closely connected, since translation of information and labelling of medicinal products to national languages is not a problem for big markets, but is considered unfeasible for small markets. The size of a market is an obvious reason why pharmaceutical companies are not willing to accept the extra costs involved (pharmacovigilance, translations, scientific service, pricing, country specific information, etc.) for markets that cannot sustain profitability.

The combination of different prices and parallel import/export may be one of the reasons for availability problems in certain markets that is not due to the size of the market.

The report is looking at the Medicine availability problems connected to the different marketing authorisation procedures.

The consequences for the patients will depend on the severity of the illness and the availability of generic or therapeutic alternatives.

Chapter 2 is giving the overview about the currently available regulatory environment and is also looking at the main difficulties in implementing the provisions in Member States.

It gives also the overview about the initiatives to address the problem of medicines availability by the European Commission, by the EMEA and by the Member States.

In chapter 2 of the report we can see what has been indicated by the industry as the main constraints and limitations to the drug availability.

Chapter 3 is the part of conclusions and recommendations about the availability of human medicinal products. The part of recommendations is divided into two subparagraphs: first includes necessary decisions on national level and improving the implementation of the current legislative framework, the second part are the possible ways (but not all) for changes to the legal framework.

There are also six appendices to the report, the main ones are giving the overview of the countries and examples from the Member States illustrating the issue of availability problems of medicinal products.

The report concludes that patients` needs should be the ultimate priority of the pharmaceutical *acquis*. This is not always entirely compatible with the philosophy of the *acquis* concerning exclusive applicant's right to choose "suitable" markets for marketing their products. The industry's decision to market on a particular market is unconditionally supported by the *acquis*. Incentives for industry are not accompanied by obligation concerning availability. Industry seems to be always in a dominant position, particularly in the case of small markets.

The further action by the EC and by the MSs who have identified the problem is necessary. The report gives some possible ways for that.

*The members of the Task Force are very grateful to all the colleagues from national competent authorities of Europe, from the EC and the EMEA who helped the group with gathering information or giving good advice for the Report.*

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\* In the context of this report references to "medicinal products" mean human medicinal products, unless stated otherwise.

\* In the context of this report references to "European country" mean EU countries and Iceland, Norway, Liechtenstein, unless stated otherwise.

## Chapter 1. Introduction, Background and Current Situations

The market of medicinal products in the European Union is a highly regulated area. Differing from the idea of “New approach”, medicinal products are regulated differently and their entering to the market is not only the responsibility of their manufacturer. The authorisation for placing on the market is granted by the regulatory authorities of the Member State or the European Commission after an assessment by relevant expertise. However, this authorisation can only be issued after the manufacturer has applied for it. This concept works well in an ideal world where the manufacturers are interested to place their products equally to all the markets, but in reality this may not be the case. If such situation happens, we can see that there are not enough instruments for the governments to handle and solve such situations. It is generally expected to be quite obvious that manufacturers of medicinal products are interested in selling their products. What are then the reasons for the lack of availability of some medicinal products on some markets?

The Task Force (TF) on availability of human medicinal products was established by the Heads of Medicines Agencies MG in March 2007. The establishment of the TF was followed by the identification of the problem of unavailability in the sector of human medicinal products, especially in small and medium-size countries. The problem has been raised by the regulators, physicians, pharmacists and other users of medicines: there are unmet needs of human medicinal products in several countries. Problems in the availability of an adequate range of medicines have different origin and consequence for the public health in the concerned countries.

The aim of the report is:

- to look at the current situations concerning the availability problems of medicinal products in the Member States;
- to highlight the problems with implementing the current legislation;
- to look for the possible solutions for the availability problems.

This report does not examine in detail the issue of the low interest of companies in developing medicinal products for certain diseases.

The report uses case studies and the situations in different Member States have been analysed. Some cases may apply to more than one Member State and others may be more specific.

The issues related to pricing and reimbursement must be addressed separately from the Community provisions on marketing authorisation procedures and their implementation. The problem of the unavailability of an authorised product on the market of a Member State may be the consequence of some reimbursement decision of the government not in favour of the marketing authorisation holder (MAH).

For the clarity, the following terms are used:

*Non-availability of a medicinal product* – the situation in a Member State where the company has not applied for a MA of a certain product or a product with a valid MA is not placed on the market or there is a discontinuity in the availability. The situation may be further described as:

*Temporary* (mostly unintentional): the situation is mainly caused by difficulties in manufacturing or wholesaling. It may be short-term or long-term. Often companies are able to inform the regulatory authority and stakeholders on time. Sometimes the regulatory authority in MS only gets the information about missing medicines from pharmacists or physicians. If the company has manufacturing difficulties and the demand from the market is greater, the smaller markets may find themselves at the bottom of the priority lists for supply.

*Constant* (mostly intentional): the situation is caused by the decision of the company not to apply for marketing authorisation or not to put a product on a market in a Member State. If the product is necessary for the users, the drug regulatory authorities in these countries use several options for solving the situation. These will be discussed in this report.

*Absolute*: The situation is caused by the low interest of the company in developing or manufacturing a necessary medicinal product. This situation is not covered by this report.

The main reason for the intentional unavailability of some medicinal products seems to be the size of the market. Small (and/or medium size) markets are not so attractive for industry from an economical point of view. Some other relevant factors besides the size of a market should be taken into consideration when assessing problems of availability of medicinal products.

The list of missing products varies between the Member States. The seriousness of the health problem derived from unavailability of some medicinal product depends on several factors, e.g. quick information exchange, adequate legal possibilities and fluent procedures. Probably no Member State is worried about missing “me-too” or similar products; the representatives of competent authorities have indicated missing life-saving or essential medicinal products. The TF admits there are Member States who have not experienced any low interest of companies in making their products available on their market.

The unavailability of some medicinal products poses a real threat to public health and welfare. The lack of authorised medicines poses problems for patients, physicians, consumers and governments. These include:

- Public health concern if patients are untreated or treated with an unauthorised or an unsuitable product or product about which the information to the regulatory agency is limited (licensed import of unauthorised products, ‘off-label’ use of products).
- Public health concern about unclear procedures for pharmacovigilance of unauthorised products used by a physician for an individual patient.
- Increased costs for the governments and hospitals to keep the procedures of purchasing the unauthorised products for individual patients.
- Increased costs for patients as in several countries unauthorised products used by physicians for individual patients are not reimbursed under usual conditions, which mean untreated conditions for lower income patients.
- Public health concern rising from untreated or ineffectively treated infectious diseases (e.g. tuberculosis).
- Public health concerns where patients and institutions do not find medicinal product authorised in the MS, and revert to obtaining directly the medicine for

personal use over the internet and getting medicine, which might be counterfeited. The rising demand for such medicines motivates illegal manufacturers/suppliers.

The availability of human medicinal products on small markets is a public health concern and thus requires attention. Since the problem concerns public health, it is necessary to define the problem and to propose actions to be taken in favour of patients.

In order to define the problem it is necessary to keep in mind the following question:

- Are the availability problems of medicinal products only a problem of small markets?
- What defines a small market?
- When does a problem of availability become a public health issue?
- What defines the interest of pharmaceutical companies to market medicinal products?
- What does the existing EU legislation offer for improving availability of MPs?
- What is missing from the existing EU legislation that would ensure proper availability of medicinal products?
- What could be done to improve the situation?
- Does the current situation of lack of availability of medicinal products represent a true single European market for medicinal products in the different EU Member States?

These issues will be discussed in the report.

The availability of medicinal products is a strategic issue for HMA, which affects not only small countries, but also medium-sized ones and eventually others. This is a European public health problem and a common and coordinated response is needed.

## **1.1. Unattractive markets for the industry**

The main reasons for a country being an unattractive market for the pharmaceutical industry are:

- a. Size of the market
- b. Language of the country, or some country-specific requirement
- c. Need for upgrading the dossiers in MS that joined the EU in 2004 onward

The main reason for the industry not to put their products on the market in a Member State seems to be the size of the market. Small (and/or medium size) markets are not so attractive for industry from economical point of view. A short overview about the MS is given in the Appendix 1.

Many of essential medicinal products were developed decades ago. This results in a situation where marketing authorisation documents from companies and also assessment reports from Member States might not be in line with the present requirements in the *acquis*. The availability problems in smaller MSs are a result of these reasons. There are several cases in European countries in which many of the most current medicinal products are available, but the country is simultaneously missing several essential medicines, whilst they are available in other countries. In order not to go through the procedure of a full update of the dossier, the companies chose not to authorise the product in a new EU Member State. This results in a lack of several essential medicines in the smaller new MSs.

There are some common and general availability problems in small countries. No local R&D pharmaceutical industry is present in several MS. The potential of the local generics industry is small; meaning the needs of the EU MS are covered only by medicinal products coming from other countries within the EU or outside the EU. In general, economically unattractive countries are neither selected in the MRP or DP procedures as Reference nor Concerned Member States. If they are chosen and marketing authorisation is issued, the launch of the product will often not happen for reason such as the lack of labelling in the national language.

### **1.1.1. Size of the market and national language**

- These parameters are closely connected, since translation of information and labelling of medicinal products to national languages is not a problem for big markets, but is considered unfeasible for small markets.
- The size of a market is an obvious reason why pharmaceutical companies are not willing to accept the extra costs involved (pharmacovigilance, translations, scientific service, pricing, country specific information, etc.) for markets that cannot sustain profitability.
- It is difficult to get country specific packs for small countries. Some companies are willing to do a joint pack but if the smaller MS asks for any requirements which differ, or which interpretation is different from the joint pack, it may end up without the product being registered. Making the variations to the multi-language packages is complicated and need fluent co-operation also between the MSs.

- The introduction of any country-specific information (a blue box for example) decreases the motivation of the company to make the product available).
- Although repackaging facilities are easily available, many companies refuse to make use of them because of the extra costs incurred or because of company policies that do not allow the handling of their products by third parties.
- Many products, particularly products for hospital use or for rare diseases are purchased in very small quantities and MAH are not interested in adopting local packaging or PIL or to obtain/renew their marketing authorisations. At times they even refuse to supply the pack as supplied in another EU MS or may want to supply the export pack.

### **1.1.2. Dossier upgrade**

The so-called “upgrade of the dossiers” was the initiative taken by the EC to achieve the objective (or later for the countries with transitional period) that all the medicinal products in new MS would be in line with the requirements of EU on 1 May 2004. The initiative was not carried on for old MSs. On several occasions in the 1990s it happened that the generic product entered the market of the newly independent states of an Eastern European country before the originator. This created a very difficult situation in these Member States for the upgrade initiative. The net effect of the upgrade exercise before 1 May 2004 was a further significant challenge to the availability of medicines for authorities having to withdraw authorisation of medicines without upgraded dossiers. Few sponsoring companies were willing to invest the money necessary to generate the required data to support the upgrade of the original dossier. The added effect of the regulatory reviews in each MS as well as the elaboration of additional legislative standards (e.g. environmental impact standards) led to many medicines with limited sales potential being withdrawn or having their indications reduced to support only the main indications. In countries where there was no registration prior to accession such as Malta, getting a dossier that was in line with the EU requirements was still a problem because some of the dossiers of older products had not been updated in the EU 15 and the companies did not want to update the dossier for a small market.

Since early 2001 massive efforts were undertaken to upgrade dossiers of medicinal products circulated in the 10 new MS (mainly through the renewal procedure). It was evident that the dossiers of a great number of medicinal products circulating in some of these countries, although of European origin, could not be successfully upgraded in accordance with the harmonized legislation (based on relevant Directives).

It was also evident that the dossiers were not updated in the “old 15 MSs”, although the products were still available on these markets.

Experience also showed that the repeat-Mutual Recognition Procedure was not used extensively by MAHs for old and well-established medicinal products, in order to upgrade and harmonize dossiers in the new Member States. In Cyprus for example, only eight products were issued Marketing Authorisations (MAs) through the repeat-MRP. Various meetings that were held with the industry, in the framework of Pan European Regulatory Forum (PERF) and other EU-organized meetings indicated that the industry, with the exception of a limited number of products, was not willing to follow the repeat-MRP for old products circulating in the new Member States.

## **1.2. Differences in prices between the Member States, parallel export/distribution**

The combination of different prices and parallel import/export may be one of the reasons for availability problems in certain markets that is not due to the size of the market. If a centrally authorised medicinal product is not actually placed on the market in a Member State, it could be parallel distributed into the country. For medicinal products, authorised through the decentralised route, parallel import of the product could offer access to the medicinal products. It may easily happen that the medicinal product will be taken from the smaller market where it might have lower price and parallel imported into bigger country where the price of that product might be higher depending on the local price scales. More typical is the situation where companies are not wanting to differ prices (lower prices for countries with lower possibilities for health expenditure) to avoid parallel export and this makes some countries to face overly high prices for medicines to afford them. As has been said already, it is most profitable for a company to sell on bigger markets anyway.

Here are some examples describing the situation:

- Parallel export is an increasing problem in Norway; the situation is close to unavailability, and not actual lack of a product so far. The wholesalers have a duty to deliver within 24-48 hours, and the agency has recently reminded them that parallel export is only possible after being sure that normal demands in the Norwegian market will be met. The agency is considering a change in the regulation for wholesales to strengthen this.
- Cyprus does not face direct problems with parallel distributions. Nonetheless an indirect problem is faced, since a quite large volume of parallel exports are affected from Greece to other Member States with higher prices and therefore quantities available for Cyprus may be reduced.
- Malta does not have a direct problem with parallel export. However because most of the products placed on the market are UK and Irish packs the prices on the local market may be made equivalent to those in these countries to prevent parallel export.
- In Spain parallel export is a main cause of availability problems. In Spain the parallel trade of medicinal products has a special perspective in relation with other EU countries and is sometimes creating a serious public health problem because of induced shortage, in some cases involving products with no therapeutic alternative. Spain is mainly an exporter in parallel trade, because of the lower prices at the Spanish medicines market are due to price intervention by the Ministry of Health. The Spanish medicinal products are sold by local wholesalers to other countries where the price of those products is higher and at the same time the MAHs, aware of this situation, provide to the wholesalers quantities of the medicinal products in relation to the foreseen Spanish consumption to avoid parallel exportation. This ends up with a shortage of medicines at the Spanish pharmacies. Because of these shortages, patients do not find the prescribed medicine and this even leads in some cases to changes of treatment or even treatment interruptions. As the occurrence of these situations is increasing, the problem is becoming a national issue.

### **1.3 Medicine availability problems of different MA procedures**

There are four procedures in force that can be used for the submission of a marketing authorisation dossier in order to obtain a Marketing Authorization in the EU:

- a. Centralized Procedure (CP).
- b. Mutual Recognition Procedure (MRP)
- c. Decentralized Procedure (DCP)
- d. National Procedure (NP)

In compiling the report the attempts were made to find out if there were different availability problems depending on the procedure used.

#### **1.3.1. Centrally Authorised Products (CAP)**

For many of the applications for New Active Substances, the Centralised Procedure will be used, delivering a Marketing Authorisation valid throughout the EU. Probably there are Member States where all the CAPs are marketed. The problem arises when medicinal products, which have received an European Marketing Authorisation, are not being actually marketed in a Member State. Often it is not a logistical issue of supply, but the decision of the company not to prepare the authorised packages in local languages and not to make investments into local distribution schemes. Some companies deem that where volumes are small it is not feasible to produce a batch of a country-specific pack and the supplies placed on the market are parts of batches for other Member States. Competent authorities in MS are approached by the companies asking to market the product in English or other language packages. In more serious cases, the drug regulatory agencies are simply caught between two choices: the package in whatever language or lack of the product on the market. Legally, the CA in MS can't make these kinds of decisions; this is not under its competence. Practically, these health issues must be solved, and very often they need quick solutions by CAs.

The EMEA is contacted time to time in order to accommodate some proposals. There are, at least, some possibilities: to have multi lingual packaging, but also to put stickers on packs in the national language which is acceptable according to the EMEA. The EMEA has not the power to decide for the MSs about possibilities not to use local languages. This is an issue for the MSs themselves and may be to be discussed between the Commission and the MSs because the EMEA can only say that the legislation applies. The EMEA needs to be informed as responsible for checking the labelling and leaflet, but the decision is for the MSs, not for the EMEA.

The EMEA has informed the companies that the approach of overlabelling/affix packs with other languages is normally only acceptable in the context of Parallel Distribution. They have also said that if it is not the case, the overlabelling of packs from another market to a different market should only be considered for an emergency situation e.g. where there is a product supply shortage. In this situation the MAH must ensure that the repackaging operation is performed under the responsibility of the Qualified Person provided that all outer and inner labelling and patient information leaflets in the language of the MS concerned are in accordance with the latest annexes to the Community marketing authorisation. The packaging site in charge of the repackaging operation should be registered in the marketing authorisation application and should perform the activities in accordance to GMP requirements. In addition, the EMEA has informed the MAHs that the agreement from the supervisory authority receiving such overlabelled packs on their market should be foreseen by the MAH.

All medicinal products receiving an Orphan designation are authorised through the Centralised Procedure. The orphan medicinal products are a specific case that has been stated in article 63(1) third para of the Directive 2001/83/EC which can be distributed with only one of the languages if it's justified. The EMEA is open to any justification.

Here are some examples describing the situation:

- At the end of 2006, approximately 322 centrally authorised medicinal products (trade names) were in the central register. 37% of them were sold in Estonia within 2006.
- A little less than 40% of all products (product names) with MA are actually put on the market in Norway. One reason may be that one product may have several MA under different names and only one name is marketed in Norway.
- About 14% of active substances authorized through the CP are circulating in Cyprus.
- Malta and Estonia have indicated a problem that centrally authorized products are not placed on the market if they are not reimbursed.

### **1.3.2. Mutual Recognition Procedure/ Decentralised Procedure (MRP/DCP)**

The Mutual Recognition Procedure has to be used if the product is already authorised in a Member State. The MRP can also be used for new products. The DCP can only be used for products not having a MA in any EEA country (new products). The MRP starts with a National Procedure with the chosen Reference Member State (RMS). To run a MRP a company needs at least a RMS and at least one CMS, the number of CMSs can vary from one MS to all MSs. Ideally, all the MSs could be involved; in reality this is rarely the case. Not all the products entering the EU market through MRP/DP have the potential to cause a serious health problem if missing; however, sometimes it is the case.

It has happened that the RMS was a small country chosen because of lower fees or for more streamlined procedures, and after mutual recognition by all the other Member States the only country where the product would not be marketed was the RMS.

The availability problem arises if those medicinal products, which have received a Marketing Authorisation, are not being actually marketed in a Member State or a country is not chosen to participate in the procedure.

Old, cheap products circulating in some Member States cannot follow the repeat-MRP, because of (a) high fees involved vs. low sales in small markets, (b) updating old dossiers by the MAH, so as to be able to initiate the Repeat-MRP, (c) MAHs have no obligation to register products.

Here are some examples describing the situation:

- Less than 50% of the product names with a MA are put on the market in Norway. One reason for this may be that they have not been able to have an agreement with

the pharmacy chain or the organisation responsible for the contracts for the hospitals.

- Repeat-MRP was not used adequately so that harmonized medicinal products could reach the markets of the new MS (Only eight products were issued Marketing Authorisations (MAs) through the repeat-MRP in Cyprus). A recent survey (April 2007) within the CTS showed the following results:

Period 1 Aug 2004 to 31 Dec 2006:

Total MRP/DP Applications Finalised (New and Repeat Use): 2,285

Cyprus as CMS: 269 (11.8%)

### **1.3.3. National procedure (NP)**

National procedures concern medicinal products that are only going to be marketed nationally. These are mostly generics and herbal medicinal products. For generics, the national procedure is used by local manufacturers. It may also be used by other manufacturers who want to market a product with a different indication in that specific country compared to the indication proposed in the MRP or DCP. They create a national company that then applies for a MA. It is a way of working around the MRP and DCP procedures, but may be valuable because it may secure generics in a small country.

In a few, very seldom, cases a local manufacturer provides a medicinal product with an active substance that are only used in that country. Withdrawals of the MA or temporary availability problems are more serious in these cases, because there are no other suppliers.

### **1.4. Temporary availability problems**

The situation is mainly caused by the difficulties in manufacturing or wholesaling. It may be short-term or long-term. Often companies are able to inform the regulatory authority and stakeholders in time. Sometimes the regulatory authority in the MS only gets the information about missing medicines only from pharmacists, physicians or patients. If the company has manufacturing difficulties and the demand from the market is bigger, the smaller markets may find themselves at the end of the priority lists of supply.

Probably all countries have experienced the cascade of problems when supply of a product is interrupted: the CA usually recommends another product with a similar therapeutic mechanism, the demand for this product exceed expected sales, and supply can not be increased because of the production plans of the companies.

- A problem exists in Iceland regarding wholesalers. There are no real wholesalers in Iceland, but only distributors who distribute the medicinal products for the MAH (or his agent in Iceland). These distributors do not order or own the stock- this is handled by the MAH or his Agent. When there is an availability problem the MAH / Agent needs to act and this adds one additional link to the chain which can cause even more delays in solving the problem.

National reimbursement and pricing arrangements may become a problem in cases where a medicinal product has been authorised and it may not been marketed unless a price has been fixed by the Ministry of Health or another competent body. A patient who urgently needs this certain product might have to wait for the authorised product until it has received the price because it has fallen out of the compassionate use scheme.

### **1.5. Consequences of availability problems of medicines**

If the missing medicinal product is of high importance, it creates problems for patients, physicians, pharmacists, regulators and health budgets of the countries. The impact of drug shortages on patients and physicians is enormous, especially in the treatment and prevention of serious and/or urgent conditions. In many cases, the lives of patients could be at risk. Several countries have stressed that the availability problems of medicinal products also have political consequences in the countries.

The consequences for the patients will depend on the severity of the illness and the availability of generic or therapeutic alternatives. The use of unauthorised products brings safety, quality as well as financial problems for patients. Who is responsible for pharmacovigilance of unauthorised products? This is a legal issue and of great public health concern.

The consequences for physicians are that they lack essential drug to treat the patients. They may need to use other medicinal product which is suboptimal in treating that particular patient. The process of applying for an exemption for licensing creates more administrative burdens for the physicians. It is time consuming for physicians to find a different or another product for his patient and sometimes the solution is not optimal for the patient.

The consequences for pharmacists. Those are the ones meeting the patients demand in a temporary non availability. They have to contact the physician for an alternative solution, inform the patients why the drug is different from the physician's prescription etc and it is time-consuming.

The consequences for regulators may be described as resource-demanding. If the product necessary in the MS is available in some other country, the competent authority must handle the procedures for solving the availability problem. It may simply be the procedure of communicating with physicians and finding alternatives from the local markets. But it may be also the procedure for making the products without marketing authorisation available in the MS. At the moment we can say that MSs are having different viewpoints on handling the situations, starting from the totally free decisions of the physicians to order these products under their responsibility and ending with the full control of the CA over these cases in Member States.

Here are some examples illustrating the situation:

- The medicinal products used according to Article 5 of the Directive 2001/83/EC are not generally covered by the health insurance in Estonia, i.e. in most cases the whole price must be paid by the patient himself.
- The exemption for licensing regulation is considered useful for single patients and hospitals in Norway. It is partly a notification system, partly an application system available in Norway. It is very important to secure treatment for patients in a small market like Norway. On the human side there are 44 000 notifications/applications each year. However, these products are much more expensive than if they had been put on the market, and there are more difficulties with reimbursement for the

patients also. This applies for Iceland as well. The Icelandic Medicines Control Agency received 11.098 notifications / applications in 2006.

- The CA in Cyprus indicates that patients and physicians in their attempt to cover their needs are importing medicinal products from abroad or from the internet or from the northern part of Cyprus, occupied by Turkey. The quality of these products cannot be safeguarded; language and PIL obligations cannot be controlled.
- The CA in Cyprus indicates also that political consequences are also significant since drug shortages are creating public health problems, limiting the choice of therapeutic schemes and leading to the use of more expensive drugs, particularly due to the fact that old well-established and cheap medicinal products are no longer available. The Media covers the matter on a regular basis and Medical and Pharmaceutical Associations as well as consumers and patients' associations are complaining and applying pressure on the Ministry of Health to take such measures as to make available to Cypriot patients the same choice of medicinal products that other EU citizens have access to.
- The CA in Malta indicates that the lack of availability of medicines following accession and the increases in prices of medicines as a consequence has become an issue of great public health and political concern. The lack of availability of medicinal products results in patients buying products directly from other countries or over the internet, thus jeopardizing the safeguarding effect of the EU regulatory framework. Wherever possible, essential products, which are not available on the market, are being sold by the National Health Services. The National Health Services often face the problem that they do not find supply of products from local agents and MAHs refuse to supply the NHS directly.

## Chapter 2. The Currently Available Regulatory Environment

### 2.1. Current legislative and regulatory measures related to the availability in the Community law

The area of medicinal products is governed in the EU mainly by Directive 2001/83/EC relating the medicinal products and Regulation (EC) 726/2004. The fundamental premise of the Directive is clear. Article 6 of Directive 2001/83/EC requires that medicinal products are authorised before they are marketed in the Community.

*No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive or an authorization has been granted in accordance with Regulation (EEC) No 2309/93 (726/2004).*

.....

*1a. The marketing authorisation holder shall be responsible for marketing the medicinal product. The designation of a representative shall not relieve the marketing authorisation holder of his legal responsibility.*

There are four procedures in force that can be used for the submission of a marketing authorisation dossier in order to obtain a Marketing Authorization in the EU:

1. National Procedure (NP)
2. Mutual Recognition Procedure (MRP)
3. Decentralized Procedure (DCP)
4. Centralized Procedure (CP).

Additionally, there is the possibility to use the Parallel Import (PI) procedure.

The availability of medicinal products has been addressed in the recent review of medicinal products legislation and is reflected in a number of specific provisions of the Directive 2001/83/EC and the Regulation (EC) 726/2004:

#### 2.1.1. Specialties provision: Article 5 Directive 2001/83/EC .

*1. A Member State may, in accordance with legislation in force and to fulfill 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.*

*2. Member States may temporarily authorise the distribution of an unauthorised medicinal product in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.*

*3. Without prejudice to Paragraph 1, Member States shall lay down provisions in order to ensure that marketing authorisation holders, manufacturers and health professionals are not subject to civil or administrative liability for any consequences resulting from the use of a medicinal product otherwise than for the authorised indications or from the use of an unauthorised medicinal product, when such use is recommended or required by a competent authority in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm. Such provisions shall apply whether or not national or Community authorisation has been granted.*

4. *Liability for defective products, as provided for by Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States, concerning liability for defective products, shall not be affected by paragraph 3.*

**2.1.2. The Sunset clause: Article 24, Paragraph 4, 5 and 6, Directive 2001/83/EC;**

4. *Any authorisation which within three years of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State shall cease to be valid.*

5. *When an authorised product previously placed on the market in the authorising Member State is no longer actually present on the market for a period of three consecutive years, the authorisation for that product shall cease to be valid.*

6. *The competent authority may, in exceptional circumstances and on public health grounds grant exemptions from paragraphs 4 and 5. Such exemptions must be duly justified*

**2.1.3. The provision on Continuous supply: Article 81, second Paragraph, Directive 2001/83/EC;**

*The holder of a marketing authorisation for a medicinal product and the distributors of the said medicinal product actually placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered.*

*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.*

**2.1.4. The Cyprus clause: Article 126a, 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 authorize 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.*

3. *Before granting such an authorisation a Member State shall:*

*(a) 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) request the competent authority in that State to furnish a copy of the assessment report referred to in Article 21(4) and of the marketing authorisation in force in respect of the said medicinal product.*

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.*

**2.1.5. Compassionate use for patients with chronic, serious or life-threatening disease: Compassionate use through an approved clinical trial protocol: Reg (EC) No 726/2004**

Compassionate use programmes are intended to facilitate the availability to patients of new treatment options under development.

National compassionate use programmes, making medicinal products available either on a named patient basis or to cohorts of patients, are governed by individual Member States (MS) legislations. Compassionate use implementation remains the competence of a MS.

Article 83 (1) of Regulation (EC) No 726/2004 introduces the legal framework for the provision of compassionate use in the European Union for medicinal products that are eligible to be authorised *via* the Centralised Procedure, stating that “*by way of exemption from Article 6 of Directive 2001/83/EC, MS may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and 3(2) of Regulation (EC) No 726/2004 available for compassionate use*”. Article 83 of Regulation (EC) No 726/2004 on compassionate use is complementary to national legislations and provides an option to MS who wish to receive a CHMP opinion regarding the conditions for compassionate use of a specific medicinal product which falls within the scope of Article 83(1) and 83(2).

The use of Article 83 is applicable to unauthorised medicinal products for human use falling within the scope of Articles 3(1) and 3(2) of Regulation (BC) No 726/2004, without prejudice to the subsequent marketing authorisation route as required or permitted by that Regulation.

In addition, each of the following specific criteria should be fulfilled:

- The medicinal product is to be made available to patients with a chronically or seriously debilitating disease, or a life threatening disease, and who cannot be treated satisfactorily by an authorised medicinal product in the European Union,
- The compassionate use programme is intended for a group of patients,
- The medicinal product is either the subject of an application for a centralised marketing authorisation in accordance with Article 6 of Regulation (EC) No 726/2004 or is undergoing clinical trials in the European Union or elsewhere.

In accordance with Article 83 (6) of Regulation (EC) No 726/2004, the EMEA is responsible for keeping an up-to-date list of the opinions adopted on a public register available on the EMEA website.

The guideline has been finalised with input of the Commission for interpretation issues. Till now no requests have been introduced to the EMEA.

## 2.2. Difficulties in implementing the provisions in MSs

We admit that the Community law gives some possibilities of handling problems of availability. There are several factors within the legislative regulatory framework that affect the availability of medicine within the Community.

Articles 5 and 126a of Directive 2001/83 may be used in case of a need for unauthorised products. In the situation where a product is authorised, but not placed on the market, the practical solution is to (parallel) import it or buy it elsewhere. Furthermore, Article 81 provides that MA-holders have to ensure the supply to the market. The observation is made that Article 81 seems to be difficult to enforce, but this is the mechanism as provided by the Directive. If too much pressure is used, the MAH will withdraw the MA and in that case even parallel import is no longer possible. According to the ECJ jurisprudence, products may still be imported in parallel even if the MAH withdraws for reasons not related to public health. The issue is that there may not be an agent/wholesaler who is interested in doing parallel importation as it can prove to be difficult.

In the following section, reasons why this does not work out in practice are discussed.

### 2.2.1. Specialties provision: article 5 (1) Directive 2001/83/EC .

It is not absolutely clear if Article 5 is applicable for authorised products or is it applicable only for unauthorised products. Some Member States are using this article to handle the availability problems of Centrally authorised products. Not all share this interpretation and consider this case as a distribution issue only.

Art 5 (1) concerns the supply situation. It is considered to be applicable to authorised as well as unauthorised medicinal products for which there must be a therapeutic need. Representatives of some Member States are of opinion that it should be used as extensively as possible in the case public health issues are at stake. In many MSs physicians are allowed prescribe any medicines for patients under their care, in some Member State it is under control of a competent authority, in others there is no system for monitoring or controlling this process. Some MSs have added to their national legislation the right of the agency to withdraw the authorisation if serious problems occur relating to their quality, safety or efficacy of the medicinal product, including serious adverse reactions. In several MSs the system favours the doctor and patient; if a doctor wants to use a certain medicinal product (authorised or unauthorised), a permit can be obtained from the CA. This is because in article 5 the word `supply` is stressed.

There seems to be different viewpoints in different MS and there are still unclear points in the implementation of the article, including:

- Is it really for named patients or can it be used anonymously (for categories of patients) too?
- Is it possible to import a product on a named patient basis, which is already authorised in the Member State concerned?
- Is it possible to use it for hospital products?
- Can it be implemented for CAP not available in the market?
- Is it possible to supply from a wholesaler abroad directly (i.e. through post) to physician or patient?
- Is it necessary to involve a pharmacy in the supply chain?
- What is the responsibility of the physician prescribing unregistered medicines?

It should be kept in mind that there should not be “hidden” marketing of the product or circumvention of authorisation, fees, etc under this paragraph.

#### 2.2.2. Article 5 (2) Directive 2001/83/EC.

There is no data available how many MSs have implemented and are using the Article. This may be useful for antidotes, and for drugs used in special epidemics (i.e. an pandemic situation).

#### 2.2.3. The Sunset clause: article 24, paragraph 4, 5 and 6, Directive 2001/83/EC;

The sunset clause provision is easy to circumvent in practice and difficult to implement in reality. It does not truly guarantee the availability of medicinal products to meet public health need at all times.

The opinions on the usefulness of the Sunset Clause with respect to access to medicines are divided: many delegations in Emacolex felt that in fact the effects would be rather limited. If the Marketing Authorisation Holder is, for his reasons, not inclined to market a product in a specific market, the sanction of revocation of the Marketing Authorisation does not offer a solution: if there is no MA, the product cannot even be parallelly imported.

It is quite easy to fulfil the requirement for the MAH – even if 5 packages have been made available, the CA can’t make any sanctions. But the real availability has not been guaranteed.

The sunset clause is counterproductive – if the marketing authorisation is withdrawn then the regulator is officially banning the product from being placed on the market. There are ways of circumventing the sunset provision. There is an opinion that “Sunset clause” does not support supply on the market, because in the end the MS loses the medicinal product anyway.

#### 2.2.4. The provision on Continuous supply: Article 81, second paragraph, Directive 2001/83/EC;

During the EMACOLEX Montreux meeting much input was contributed to discussions on the ‘continuous supply’ provision. The first observation concerned the text of the article, where the scope is limited to those medicinal products that are actually marketed in a Member State (see Article 81, second paragraph). This means that the article is not applicable to medicinal products that have never been authorised on a (national) market.

The second observation concerned the legal ‘efficacy’ of Article 81. Since the article does not clarify to whom it is addressed, it seems difficult to enforce it. In a situation in which a product has been marketed before, but is not available any more for the patient (or in the pharmacy), who would be the (legal) person to be addressed by the authorities? Would it be the responsibility of the Marketing Authorisation holder or could it be someone in the distribution chain?

This lack of clarity about the addressee of the norm in Article 81 has been the reason that in some countries the provision has not been transposed into national legislation. The nature of a marketing authorisation is that of an authorisation: a legal act allowing a company to do something that is prohibited otherwise. It cannot be considered as an obligation. Therefore, the responsibilities of the holders of marketing authorisations, even with respect to Article 81, cannot be linked to the public health concern of having access to all necessary medicinal products. It is difficult that it states that there is an obligation to supply the market at the moment the MA is granted and that there are no tools to compel a company to do so.

The suggestion has been made that a penalty might be a solution. The question is who would be responsible for not marketing the product: would it be the MA-holder, the wholesaler or the government? The opinion has been raised that an MA is an administrative act that removes obstacles to perform certain activities. Once the MA is issued, the holder is free to use or not to use the authorisation. An issue with respect to Article 81 is the burden of proof, if an MAH wants or does not want to use the MA.

Under EMACOLEX, a questionnaire was sent out in 2006 to identify the situations regarding public service obligations in Member States. The outcome (11 answers) showed that some MSs have a sort of public service obligation for wholesalers, but no specific implementation or sanctions; some MSs have no public service obligation for wholesalers yet and some MSs have public service obligation for wholesalers with specific implementation, i.e. an obligation to have a certain stock or obligation to fulfil the orders, etc.

#### **2.2.5. The Cyprus clause: Article 126a, Directive 2001/83/EC.**

With regards to the Cyprus clause, experience is very limited. A problem that could be identified is the division of responsibilities if the Marketing Authorisation Holder does not register a product in a specific Member State. This Member State should, when applying the Cyprus clause, be sure who would take responsibility with respect to translation of Product Information and with respect to pharmacovigilance. The pharmacovigilance obligation and the obligation for the translation of labelling and PIL could be the responsibility of the MAH or the importer/special marketing authorisation holder. The Cyprus clause leaves the interpretation up to Member States but exposes the Member State to the possibility of court cases due to interpretation.

Some companies are not in favour of the implementation of Article 126a by a MS for their product as it might put unintended responsibilities to the company and it also may attract the attention of the EC or other MSs to the fact that the company does not want to apply for MA in that particular MS through MRP procedure because the company may not have an upgraded dossier of that product.

When a MS wants to use the clause and asks the concerned MS the Assessment Report, it may not get it because of different reasons.

Some of the countries who have used this article have pointed out the new challenge. The CA has received complaints from authorisation holders of products authorised by 126a saying that the MAH 'reprimanded' them for registering products by this procedure in that particular country and this would likely result in problems with supply of these products to the applicants. Of course, these tactics are done in a subtle way and MAHs have full liberty and no responsibility. The situation shows that the true value of provisions like article 126a is minimal and cosmetic. Unless MAHs are obliged to supply products, the problems of availability may remain.

#### **2.2.6. The requirement for the official language of labelling and package leaflet: Art 63, Directive 2001/83/EC**

The idea in the Community legislation of having all the product information in local languages of the MS is absolutely correct and justified. Unfortunately, this requirement

works well with large countries and big volumes of medicinal products, but it adds additional burden and problems to smaller markets.

Often only small quantities of product in a given presentation are sold in the different countries. As a result, the costs linked to country-specific packaging (individual packaging runs under GMP, printed packaging material, logistic handling of demands for individual markets) present a comparatively high expense in the overall cost of these medicines. Particularly in the context of the recent EU enlargement, companies have realised that switching the locally-approved products to local language packaging in line with current EU legal requirements is often not economically viable.

This problem is also reflected in the marketing of centrally authorised products (CAPs), which are marketed on average in only 30-50% of the EU markets due to the high cost of producing medicines with local language labels.

The Directive says that when the product is not intended to be delivered directly to the patient, the competent authorities may grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet and that the leaflet must be in the official language or languages of the Member State in which the product is placed on the market. It is not clear why this is not the option for the centrally authorised medicinal products.

Some EU countries have the experience that companies sometimes offer the easier option of supply of the export packs instead of authorised packages. Export packs differ from EU packs in terms of labelling and information (particularly indications and contra-indications). It is considered anomalous that after the thorough process of registration the CA has to accept export packs on the market. The MS CA has to deal with the situation if to sacrifice not having essential products on the market or to enforce regulations without any exemptions.

The Article 63 applies for all procedures including centralised procedures. Article 63(3) related to products that are not intended to be delivered directly to the patient the wording is not very clear and at the QRD it has been discussed. Not all MSs have the same point of view. This point needs more work and input from the Commission. But in any case this point is applicable to all procedures including centralised procedures.

### **2.3. Initiatives to address the problem of medicine availability (Commission, EMEA, MS, stakeholders)**

#### **2.3.1. European Commission**

The regulatory environment governing medicines is highly developed and complex. It is underpinned by Community legislation, which has been supported by scientific guidelines and pharmacopoeia monographs. Additionally, regulatory guidelines are provided in the Notice to Applicants.

The Commission representative has pointed out the following legal and regulatory tools to support medicines availability:

- Authorisation procedures
  - Centralised procedure *per se* – one single authorisation for entire EU
  - New tools – fast track, conditional authorisation, compassionate use

- The DCP and MRP
- Validity of the authorisation
  - Five years, one renewal, subsequent unlimited validity
  - Sunset clause
- Labelling and patient leaflets
  - Use of several languages (exception for orphan medicines)
  - Labelling and leaflet included in mutual recognition
- Pack sizes
  - Flexibility in pack sizes to respond to different needs
  - Possibility of co-marketing with differentiation
- Wholesalers obligations (Article 81, Directive 2001/83/EC)
  - Public Service Obligation
  - Obligation to supply
- Cyprus clause (Article 126a, Directive 2001/83/EC)
- Transparency measures
  - More information to be published
  - Information on withdrawals
  - Information on drug shortages
- Eurogeneric provision

To address the issue of drug availability, after initiative of the Commission (DG Enterprise) meetings were organised in Brussels with interested competent authorities of individual member states. These meetings were also attended by other stakeholders associations (e.g. EFPIA, EGA, GIRP, local industry associations).

In these meetings key issues on the availability of medicinal products, their impact and possible ways of resolving the problem have been identified. Such issues include the size, local characteristics and profitability of the markets, labelling particulars, the upgrade of dossiers, the local industries and distribution networks etc.

The Commission underlines that the problem on availability is not only linked to the pharmaceutical legislation. National implementation and interpretation of existing pharmaceutical legislation as well as policies on pricing, reimbursement and fees are also of great importance to explain this problem. Since pricing, reimbursement and fees are in the hands of the Member States, the Commission's role is limited in this area.

### **2.3.2. The EMEA**

The EMEA with the QRD will work on a development of a policy for the application of Article 63 of the Directive 2001/83/EC. The input from the Commission will be requested. It is possible that not all MSs would accept having the medicinal products, even only for hospital, in other languages than the national one arguing that nurses are not able to understand. If all MSs are in agreement it will be easier for the Commission to follow some proposals for the application of article 63.

The Agency has launched an 'SME Office', which is dedicated to addressing the particular needs of smaller companies. The Small and Medium size Enterprise Office represent a help for small and medium size enterprises and the translations (not packages) are prepared for them by the EMEA.

### 2.3.3. The Member States

Authorities in MSs have found various ways to assist finding solutions to the availability problems. When availability problems exist, the possible solutions are evaluated taking account of the specific case that has been met. Here are some general examples (for a full list see Appendix 3):

- Several countries have introduced a system which allows the unauthorised medicinal products to be imported and used, on the basis of a single authorisation for import and use of the agency, at the medically justified written request of a doctor or veterinarian qualified to prescribe the medicinal product for the treatment of a person (persons in the hospital) or animal treated by the doctor. The question of dividing the responsibilities and liability in this procedure for damage to health resulting from the use of the medicinal product for its intended purposes between government, agency, physician, hospital or manufacturer have been solved in different ways.
- Some countries have introduced a system which in the absence of an authorised medicinal product with equivalent effect or if such product is not available, allows the agency to grant authorisation to import and use: unauthorised medicinal products based on an application of a professional organisation of doctors for a diagnosis specified in the application; unauthorised antidotes or unauthorised medicinal products for use within the framework of national programmes. In addition some countries may also grant authorisation for the import and use of unauthorised medicinal products for use in special and identified emergencies.
- Licences for parallel import, parallel distribution. Though it should be mentioned that parallel import may cause shortages in the country of origin.
- Many countries have fee waivers or reductions of fees for national authorisation procedures for low-turnover medicines. This is also the case for medicinal products having a MA through MRP or DCP. Some countries also defer most or the entire yearly turn-over fee for niche products to keep them on the market.
- Financial or other support for research into development of suitable medicinal products.
- Pragmatic flexibility with local language requirements for packaging and information when needed.
- Common SPC and PIL for more than one country, or use of a foreign package when needed – with the PIL in national language printed out in the pharmacy.
- Marketing authorisation holders are being encouraged to include small and economically unattractive countries in MRP/DCP procedures as CMS with other Member States. There is increased direct communication with marketing authorisation holders.
- Not setting prices of medicines before they can be placed on the market.
- Some MSs have an especially dedicated website on market shortage indicating the date that the medicine will be on the market again. A few countries are looking into the regulation of parallel export to avoid temporary availability problems.
- Search of an alternative therapeutic solution under the form of another medicinal product authorised in the country.
- Alternative under the form of a magisterial preparation or subcontracting of particular magisterial preparations by an authorised person/company.
- Derogation given by the authority to the company, allowing the company to import and market foreign packaging under conditions (i.e. re-labelling of the packaging).
- Import of a medicinal product by the pharmacists, from other countries where the necessary medicinal product is authorised (an import on patient named basis).

## 2.4. Industry's view on main constraints and limitations

### Belgium

- Economic reasons - price of the medicinal product is too cheap, Belgian market is too small and it is difficult to get a reimbursement for the medicinal product;
- Difficulties to produce a medicinal product in accordance with the regulatory and quality levels requested (i.e. difficulty to find a quality raw material).

### Estonia

- The amounts of many centrally authorised medicinal products used in Estonia are very small and the company is not producing the package in local language as authorised by the Community marketing authorisation. In that case they can't sell packages in other languages, as these are not authorised by the EC for Estonia. There are two solutions: first, to use the unauthorised packages on patient-basis or, second, to make the variation to the central authorisation to allow the product to be sold in Estonia in different package. The first solution gives only a bureaucratic solution and the second one seems to be too costly for the company. Therefore, the product remains unavailable.
- The wholesalers/importers have informed the agency that several manufacturers are not selling small quantities at all.
- One example is given here about the unwillingness of the company to start the procedure of MA. There was one specific vaccine, which was decided to include into the national vaccination programme. But there were no authorised vaccines of that kind in Estonia. The manufacturer of the vaccine was contacted, but it informed the CA, that in the nearest future they are not planning to start the repeat-MRP. No other options were available, and it was decided to take the vaccine out of the national vaccination programme.

### Iceland

- Costly to buy small amounts of ingredients- price often related to volume. The producers refuse to receive MAH's inspection teams if only buying low volumes.
- Package materials sold in overly large volumes for the production needed, this applies to both PIL and packaging material, and so stocks often last for many years.
- Quality control and preparing production for small batches is relatively much more costly compared to larger batches, the same applies to updating and renewal of the MA.
- Production effectiveness is much less for a batch of 1,000-5,000 units, a common size of batch produced for the Icelandic market only, compared to batches of 10,000-20,000 units.
- Translation cost is relatively higher for smaller markets.
- For most MAHs the Icelandic market is a micro market and they are not interested. This is especially true if the MAH does not have an agent in Iceland. If a MAH has an effective agent in Iceland it helps to keep the MAH interested in the market.
- The bigger MAHs are less interested in micro markets such as Iceland.
- When a MAH sells the MP to another company it is often difficult to interest the new MAH in keeping the product on the market.

## Malta

A number of reasons for not registering medicinal products in Malta were given by stakeholders. These included:

- Marketing forces/business reasons – the Maltese market is too small and it is not considered viable to produce products with the requirements for Malta.
- Some stakeholders considered the fees for authorisations to be high.
- Lack of updated documentation for older products, which were already with a marketing authorisation in another Member State.
- The work involved in preparing documentation makes the process too laborious and not worthwhile.
- Some marketing authorisation holders are not represented in Malta.
- It's not worth registering products if they are not supplied through the reimbursement system.
- The increased risk of parallel importation of products once products obtain a marketing authorisation in Malta.

## Slovenia

The size of the market is of particular importance when defining the interest of pharmaceutical company to market the product. Regulatory rules and legal specificities also influence the interest of pharmaceutical company in marketing the product, e.g:

- patent linkage for generics,
- flexibility of national requirements (translation costs, quality control costs, etc)
- predictability of procedures because of presence of different originators, qualifying of minor/major objections regarding SPC/PIL,
- generic substitution (and its scope),
- interest in placement of new products instead of old products.

### **The main criteria of the companies for selecting a RMS in MRP/DCP seem to be:**

- Importance/size of the market within the European Union (EU)
- Integrity and standing (credibility) of the RMS to enable defence of the product against other Concerned Member States (CMS)
- Long-term partnership
- Open to dialogue
- Respecting time lines
- Consideration of future variations
- Expertise in respective medical field
- Potential for specific up-front agreements

The criteria of choice of the RMS in DCP are the same as for the MRP except the size of the market and respecting time lines as the license will be granted at the same time for all the involved Member States.

Selecting the RMS does not often mean the product will be put on the market of the RMS after granting the marketing authorisation. The situation may end with a sunset clause and transfer of the duties of the RMS to another one.

## Chapter 3. Medicines Availability in the EU – the Future. Conclusions and Recommendations

### 3.1. Conclusions

- Patients` needs should be the ultimate priority of the pharmaceutical *acquis*. This is not always entirely compatible with the philosophy of the *acquis* concerning exclusive applicant's right to choose "suitable" markets (patients?) for marketing their products. The industry's decision to market on a particular market is unconditionally supported by the *acquis*. Incentives for industry are not accompanied by obligation concerning availability. The public service obligation is irrelevant for non-authorized products. Industry seems to be always in a dominant position, particularly in the case of small markets
- Not all medicinal products are made available in the markets of all Member States. MS with small markets face significant problems of drug availability, especially with products of low volume, low price as well as specialised products indicated for the treatment of severe and/or rare diseases. Several examples from bigger MSs emphasise that there are problems regarding availability also in the larger markets, but to a different degree and of a different origin. It is important to highlight that there is an availability problem in the MSs which needs to be addressed.
- Current legislative and regulatory measures should be strengthened. In this, field agencies need instruments that prevent and respond effectively to these types of problems. Current legislation may be unclear on some points. Legislation in this domain has been intended to respond to isolated public health cases, but the reality of the situation is often different.
- Article 5 (1) of Directive 2001/83/EC is not intended for solving the problem of availability of a wide range of product.
- Article 5 (2) of Directive 2001/83/EC is usable only for situations stated in the article.
- Article 24 of Directive 2001/83/EC, a sunset clause can be avoided because of implications of the principle of global MA. The clause can be easily avoided and its wide scope can be misused. No MA for an obvious inevitable drug will be revoked because of a sunset clause.
- Article 81 of Directive 2001/83/EC cannot be implemented effectively in line with European law. The Chair of the Emacolex has drawn the attention of the HMA, stating this real problem. It is not only related to the MA legislation, but also to parallel importing, to pricing and reimbursement arrangements and strategies of different companies etc.
- Article 81 of Directive 2001/83/EC is not clear enough to be used effectively in practice.
- Article 126a of Directive 2001/83/EC is unclear, particularly concerning responsibility for PhV, variations. The experience is limited. The companies often

do not have the necessary upgraded dossiers and the CA of Member States may not have upgraded Assessment Reports, especially in the English language to provide to the MS making the request.

- MSs are obliged to participate in CP; the industry does not market on all EU markets.
- Costs of regulatory procedures do not significantly influence decisions on authorization.
- Drug availability problems impose significant risks to public health. Moreover, they create significant political problems as health professionals and patients demand full and continuous access to an assortment of medicinal products including their specific medication as well as other treatment alternatives.
- Member States are implementing country specific procedures for dealing with the issue. There might be some controversies with the existing Community legislation. Sharing of experience among Member States on best practices is not functioning very well. The legislative framework does not cover the initiatives that Member States have to take to protect public health. Some solutions in Member States increase bureaucratic hurdles.
- There seem to be no legal ways to force the pharmaceutical industry remedy these problems. An MA is, by definition, merely providing the possibility of doing something, but it cannot force one to act. Some articles in the Directive on the availability of medicinal products in that case might be only symbolic.
- The current EU legislative framework for medicinal products does not cover the principles of a true single market for all EU citizens from a public health perspective. All EU citizens have the right to the same access to medicinal products in whichever Member State they happen to live in. Medicine should be accessible for any patient who needs it. There should not be barriers to access to medicines.
- In order to gain access to otherwise unavailable medicines, patients often resort to risky behaviours that may encourage the proliferation of counterfeit products and jeopardize the principles of quality, safety and efficacy officially intended by the legislation. Such practices and methods result in adverse consequences of the legislation.
- There are not enough legal provisions to cover drug shortages in the market of Member States. Many of the provisions available are difficult to implement and enforce. Article 5 and Article 126a, of Directive 2001/83/EC are useful in dealing with drug availability problems, but not sufficient to handle massive drug shortages. The patient procedure described and Article 126a are not adequate or fast enough to cover effectively and quickly situations of massive drug shortages. The legislation is not as strong and clear as it should be. Companies may have concerns over interpretation by national authorities in Member States.

- The Directive states that when the product is not intended to be delivered directly to the patient, the competent authorities may grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet and that the leaflet must be in the official language(s) of the Member State in which the product is placed on the market. There must be clear and easy procedures how this option could be used for the centrally authorised medicinal products.
- Some Member States have adopted measures to face drug shortages that are not directly covered in the Community legislation. While this is done to protect public health, these Member States are running the risk of facing infringement procedures.
- The use of an authorised medicinal product for an indication different from the one mentioned in Section 4. 1 of the SPC (i.e. off-label use) brings along increased liability on the prescriber. This is a shifting of responsibility if the use of the unauthorised medicinal product is due to lack of availability of the authorised product on the market. .
- Acting as a RMS does not often mean the product will be put on the market of the RMS after the granting of marketing authorisation. The situation may end with a sunset clause and transfer of the duties of RMS to another one. Being active and working diligently in the European market processes, does not help small countries to get products on their own. The Competent Authorities of these countries cannot help feeling that they are only working for others.

## 3.2. Recommendations

The problem of unavailability of medicinal products has been identified as a priority issue, particularly for Member States with small and medium-sized markets, because of its effect on public health.

If patients needs, irrespective of whether they live in small Member States or elsewhere in the EU, are a priority of the pharmaceutical *acquis*, proper identification of the problem of medicine availability and looking for proper solutions are to be considered as a priority that involves the Commission, Member States and Stakeholders at the highest level.

The Commission's initiative to include the issue of availability within the remit of the Pharmaceutical Forum is a welcomed initiative. Concrete and tangible recommendations and solutions are expected and eagerly awaited from this forum. Sharing of experience among Member States that face drug availability problems should be improved. It is important that all stakeholders share a common goal to address this problem.

The choice of whether products are placed on the market of individual Member States should not be solely a matter of business viability. The public health needs of the citizens, of all Member States, need to be considered and protected. The 'incentives' given by the Paediatrics Regulations are a step in the right direction and there should be other such incentives. The Community legislation should be looked at so as to effectively deal with the problem.

Art. 126a foresees that "Not 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." Since the Article concerns the availability of medicines, it will be an additional opportunity for wider discussion on the availability problem.

Possible ways forward, indicated by the Member States are:

### **1. Taking relevant measures and making necessary decisions on national level. Improving the implementation of the current legislative framework.**

1.1. Improving the exchange of information between Member States on experiences and practices in terms of responding to the availability of medicines.

1.2. Improvement of dialogue between stakeholders on the availability of medicines.

1.3. Parallel import/distribution should be used as a solution in cases of unavailability of some medicines, but not as a mechanism for bypassing the requirements of Directive 2001/83/EC.

1.4. Implementation and use of limited possibilities provided in Article 126a of Directive 2001/83/EC for improving availability of some medicines.

1.5. Removing unnecessary administrative burdens linked to specific national labelling requirements.

1.6. Introducing language provisions exemptions for products used only in Health Care institutions.

1.7. Allowing multilingual labelling information. MSs with the same language or related languages could form an alliance to create a larger market (e.g. the Nordic countries or Greece and Cyprus) as has been done by Luxemburg and Lichtenstein, where applications for a MRA/DCP MA in one country should be sent to all countries in the group. Exemptions could be made for national languages on packaging (or use stickers). There could be an agreement between the CAs (in the designated area) that pharmacies and hospital could buy medicinal products agreed on from all wholesalers in this area.

1.8. Motivating pharmacists to widen the range of magistral formulas. Here we must keep in mind that this will not solve the problem as a whole and is more or less a niche solution. Magisterial formulas can not be produced in large scale. The quality, safety and efficacy of large scale pharmacy production need prove quality, safety and efficacy.

1.9. Establishing national early warning systems on availability of particular medicines.

1.10. Use of limited possibilities provided in the Article 81 of Directive 2001/83/EC for improving availability of some medicines.

1.11. Use of limited possibilities provided in Article 5 of Directive 2001/83/EC for improving availability of some medicines

1.12. Use of limited possibilities provided in the Article 24 of Directive 2001/83/EC for improving availability of some medicines

1.13. National pricing and reimbursement policies should be implemented considering the existing problem of unavailability of medicines. Sharing experiences among Member States concerning pricing and reimbursement would be useful.

1.14 Lower fees for marketing authorisation procedures. Although the fees represent a very low percentage of marketing costs, a reduction of fees could have a limited impact on availability of medicines.

1.15 Sharing of information between Member States on experiences and practices in terms of responding to the availability of human medicines. National initiatives on publishing stock shortages. Developing information systems linking MAH, wholesalers, pharmacies and health professionals alerting on availability problems (early warning systems). Exchange of information between the MSs.

1.16 National authorities solving problems with supplies through centralised national procurement or by giving incentives for parallel distribution in cases of shortages.

1.17 Regulatory agencies should try to establish crisis management plans for the use of alternative medicinal products within short time periods.

## **2. Proposals for changes to the EU legal framework should be focused on, but not limited to:**

2.1. Improvement of wording of the existing legislation in order to make it more clear and applicable for solving of the availability problem:

2.1.1. The scope and application of Article 126a of Directive 2001/83 as amended by Directive 2004/27 needs to be open so as to allow Member States to address their availability problems and at the same time not disrupt the balance and the spirit of the legislation within all EU Member States. Problems of MAH obligations, particularly obligations concerning PhV should be solved. The provisions of article 126a need to be clarified, particularly the responsibilities of the different players. Once a product has a marketing authorisation in the EU, the MAH should be responsible for pharmacovigilance and quality wherever the product is placed on the market within the EU - whether by registration or by article 126a or other provisions. All Member States should have an easily accessible list of their products with a marketing authorisation and the approved SPC and PIL.

2.1.2. It should be clear if Article 5 of Directive 2001/83/EC was used for named patients or anonymously for categories of patients. If used more extensively, it should be ensured that the spirit of the pharmaceutical *acquis* was not jeopardized.

2.1.3. Article 24 (4)(5)(6) of Directive 2001/83/EC should guarantee the availability of medicinal products. The existing wording linked to the concept of global marketing authorisation offers a very limited effect on the availability.

2.1.4. Article 14 of Regulation 726/04/EC should guarantee the availability of medicinal products. The existing interpretation is that any form or strength of centrally-authorized product if placed on the market in any Member State, would meet the requirements of Article 14. That allows a low availability of centrally authorised products on small and other markets (e.g. EE ca 37%, CY ca 14%, average in 30-50% of Member States). The additional dimension of the problem is that all Member States have to contribute the centralised procedure for products that will be available only on some markets. Low availability of centrally authorised products brings into question the idea of central marketing authorisation.

2.1.5. Simplification of the repeat use MRP. RMS should add a new CMS to the procedure with minimal work. Lower fees for repeat MRP in some countries. Better planning in the companies for getting maximum of MAs in the first circle of MRP.

2.1.6. Language provisions: Exemptions for hospital drugs, alternative methods of PIL information to the patients. Allow more flexibility in requirements for packages, regarding language on packages and leaflets. PIL in national language not included in package, but could be printed in the pharmacy when the MP is dispensed.

2.2. Proposal for changes to the legal framework to address the availability problem.

2.2.1. Patient needs including medicines availability should be a priority of pharmaceutical legislation.

2.2.2. Availability of medicinal products should, under agreed conditions, be treated as the obligation of manufacturers/MAHs. A penalty to the MAH is not a real solution for these cases. There should be an special obligation for the MAHs to provide the necessary medicinal products, a possibility could be the obligation to keep a reserve stock that could be regulated. Member States should have the right to identify products which are not authorised or not available on their local market and have the right to force the MAH within the EU to supply. In such case MAHs would have to supply - there needs to be an obligation on MAHs set by legislation. The MAH should be responsible for developing crisis management plans for use of alternative medicinal products should their product be unavailable. Possibilities for MSs to make a choice alternatively to the choice of MAH to take part in a concrete DCP or MRP (now only the choice of the MAH). Shortage due to production problems and MAHs obligations in this respect should be elaborated. The ability to impose penalties to MAH who have shortages (but this is counter destructive as it would result in less authorisations).

2.2.3. It is possible to link performing of clinical trials on human beings with availability of those medicinal product after placing them on the market. Clinical trial subjects are not paid for being tested. Results of those tests are obligatory part of the documentation for granting Marketing Authorisation. This puts not only moral and ethical obligation on MAH to make the medicine available for human beings. It is not only an economical category. It is patient's right. It is a wider approach than the idea of the compassionate use, that is a part of the *acquis*.

2.2.4. Measures to increase the operation of internal market of pharmaceuticals.

2.2.5. Incentives for the pharmaceutical industry should be linked to product availability.

2.2.6. Solutions given by the Paediatric Regulation concerning MAH's obligations are a step into right direction;

2.2.7. The stickers in local language for the outer package or English packages could be authorised in the CP to avoid the further problems with the companies who can't/want to market the centrally authorised products in small markets because of the small amounts in different languages.

## Appendices

### Appendix 1 – Overview of the countries

Country	Population (millions)	GDP per capita in PPS (forecast for 2007)	Size of the market of medicinal products
<b>Austria (AT)</b>	8.3	120	
<b>Belgium (BE)</b>	10.5	117.3	
<b>Bulgaria (BG)</b>	7.7	34.5	
<b>Cyprus (CY)</b>	0.8	82.8	160.6 million EUR (2006, wholesale prices)
<b>Czech Republic (CZ)</b>	10.3	76.9	
<b>Denmark (DK)</b>	5.4	125.6	2.3 billion EUR (2006, pharmacy prices; retailers, including pharmacies, + hospital pharmacies)
<b>Germany (DE)</b>	82.3	107.7	
<b>Estonia (EE)</b>	1.3	65.1	144.5 million EUR (2006, wholesale prices)
<b>Greece (EL)</b>	11.2	83.6	
<b>Hungary (HU)</b>	10.1	63.8	
<b>France (FR)</b>	63.4	107.3	
<b>Iceland (IC)</b>	0.3	131.4	19.4 million EUR (2006, retail price VAT included) (ISK 16,4 billion in 2006)
<b>Ireland (IE)</b>	4.2	140.1	
<b>Italy (IT)</b>	58.7	100.6	
<b>Latvia (LV)</b>	2.3	53.1	211.10 million EUR (2006, wholesale prices)
<b>Liechtenstein (LI)</b>	0.03		
<b>Lithuania (LT)</b>	3.4	56.6	
<b>Luxembourg (LU)</b>	0.5	255.6	
<b>Malta (MT)</b>	0.4	67.6	
<b>Netherlands (NL)</b>	16.3	125.3	4.3 billion EUR in 2004 4.5 billion EUR in 2005
<b>Norway (NO)</b>	4.7	153 (2004)	Ca 2 billion EUR (retail price, VAT included) NOK 16.4 billion (PRP) in 2006
<b>Poland (PL)</b>	38.1	52.3	
<b>Portugal (PT)</b>	10.6	68.9	
<b>Romania (RO)</b>	21.6	37.1	
<b>Slovakia (SK)</b>	5.4	59.7	
<b>Slovenia (SI)</b>	2.0	82.8	500 million EUR
<b>Spain (ES)</b>	44.5	98.3	
<b>Sweden (SE)</b>	9.1	116.1	
<b>Finland (FI)</b>	5.3	115.4	
<b>United Kingdom (UK)</b>	60.8	116.8	

- *Population 2006-2007, measured in millions of people Source: Eurostat*
- *GDP (Gross Domestic Product) per capita in PPS (purchasing power parity) Source: <http://ec.europa.eu>*

**Appendix 2** - Examples from the Member States illustrating the issue of availability problems of medicinal products

**BELGIUM**

Belgium has the experience with the following availability issues

Date	Name of the MP	Active Substance	Solution (See below)
1990	Thalidomide	thalidomide	7
01/2001	Mestinon tablets	Pyridostigmine	5
11/2002	Kemadrin solution for injection	Procyclidine	5
07/2005	Myoplégine solution for injection	Suxamethonium	5
03/2006	Apomorphine solution for injection	Apomorphine	5
07/2006	Adrenaline solution for injection	Adrenaline	6
07/2006	Pentothal solution for injection	Thiopental	4
10/2006	Levophed solution for injection	Levarterenol	6
11/2006	Mysoline tablets	Primidone	No solution found.
01/2007	Colchicine Opocalcium tablets	Colchicine	4
02/2007	Nepresol tablets	Dihydralazine	5 and 2
03/2007	TRH solution for injection	Protireline	5

When availability problems exist, the possible solutions are evaluated taking account of the specific case that has been met.

1. Search of an alternative therapeutic solution under the form of another MP authorised in Belgium (consultation of experts)
2. Alternative under the form of a magistral preparation (raw material must be available in Belgium and in accordance with the Royal Decree of 19/12/97 concerning the control and analysis of raw materials used by pharmacists)
3. Subcontracting of particular magistral preparations by an authorised person/company. This concerns preparations with homeopathic MP, allergens, cephalosporines and penicillines, all sterile preparations, risk MP, some mixed gases. In accordance with article 102 of the Royal Decree of 14/12/06 relating to the MP for human use and veterinary use.
4. Derogation given by the authority (FAMHP) to the company after consultation of the commission for advice, allowing the company to import and market foreign packaging under conditions (i.e. re-labelling of the packaging). Commission for advice: see article 128 of the Royal Decree of 14/12/06 relating to the MP for human use and veterinary use.
5. Import of a MP by the pharmacists, from other countries where the MP is authorised. This in accordance with article 6 quater, §1, 4° of the law of 25/3/64 over the MP and in accordance with article 105 of the Royal Decree of 14/12/06 relating to the MP for human use and veterinary use. This concerns an import on patient named basis.
6. Derogation given by the authority (FAMHP) to the pharmacists to authorise the import of MP from other countries where the MP is authorised when it is not possible to respect the provisions of article 6 quater, §1, 4° of the law of 25/3/64 and article 105 of the Royal Decree of 14/12/06.
7. Possibility for the King, to take all necessary measures to protect the public health. A specific royal decree must be taken. See article 12septies of the law of 25/3/64 over the MP.

The Belgian authority has pointed out the following examples of necessary medicinal products in the country - these are currently not available as a registered in Belgium:

- Anticholinergic solutions for injection (i.e. Kemadrin solution for injection);
- Levarterenol solution for injection (Levophed);
- Dihydralazine (Nepresol);
- Protireline solution for injection (TRH);
- Thalidomide.

Physicians, pharmacists and patients have pointed out the following examples of necessary medicinal products in Belgium: Iproclozide (Iproclozide Repha) and Disulfiram implant (Antabuse implant).

## **CYPRUS**

In Cyprus the population is about 770.000 inhabitants.

A survey in July 2005, showed that about 30% of the products circulating in Cyprus were not fulfilling the provisions of the legislation for Greek labelling and PIL and therefore by the end of 2005 (end of the derogation period) these products should have been withdrawn from the market, as not complying with the Directive 2001/83/EC.

Another market survey in April 2006 showed that out of the 1664 products examined, 1324 were in conformance with the Greek Labelling requirements and 340 (or 20,4%) were not.

There is a list of more than 400 medicinal products, essential for the public health, that are not available in the private market in Cyprus. These products are purchased through tenders and are originated from other Member States. Urgent needs of the private sector are covered by the Governmental hospitals. This list includes products for very serious diseases, such as cancer, poisoning antidotes, local anaesthetics, biological products, parenteral solutions, paediatric products, etc.).

The requirement for labelling and Patient Information Leaflet (PIL) in the Greek language and country specific information (e.g. authorisation number, name and address of MAH) is another major obstacle for harmonizing medicinal products in accordance with the legislation and therefore leading to availability problems. MAHs are not willing to proceed with the adaptation of the Greek language, mainly because of the small size of the market. The problem is more intense for low priced and low volume of sales products.

- Even local manufacturers in Cyprus resist adopting their products to the Greek labelling and PIL as most of their production is intended for export purposes and only a small part is intended for use in the local market.
- Products manufactured for the Greek market (same language as in Cyprus) face also difficulties to be made available in Cyprus, such as:
  - In a lot of cases information of the PIL and labelling is different for Cyprus and Greece.
  - Labelling and PIL contain country specific information (such as the name and address of the MAH and the number of marketing authorisation).
  - Dossiers of products circulated in Cyprus are originated mainly from other Member States and not from Greece (this practice was undertaken by the MAH mainly for pricing reasons). Therefore updating of dossiers was undertaken on the original dossiers of other Member States and not Greece's. Consequently SPC and PIL information may differ from those approved in Greece.

- Changes of the labelling and PIL information due to variations are not always possible to be coordinated between Greece and Cyprus (e.g. different applications dates, different timing for evaluation and approval of the variations).
- Some MAH have signed binding contracts with Greek companies for the Greek market and it is not possible for them to use Greek MAH as the MAH for Cyprus and for dealing with regulatory affairs.

Table 1 shows the number of medicinal products with a valid MA in Cyprus at the beginning of each year for the period 2000-2006 and number of products actually on the market in each respective year. The number and categories of products circulating in the private market are not sufficient to serve public health.

TABLE 1:

DATE	Number of medicinal products with a valid MA (beginning of each year)	Number of products expiring in relation to previous year	Decrease as a percentage (%) of products in 2000	Number of products actually in the market
01 Jan 2000	4855	-	100,0	3349
01 Jan -2001	4562	293	94,0	3521
01 Jan -2002	4251	311	87,5	3463
01 Jan -2003	3782	469	77,9	2890
01 Jan -2004	3291	491	67,8	2352
01 Jan -2005	2751	540	56,7	2209
01 Jan -2006	2235	516	46,0	2050 approx.
	<b>TOTAL:</b>	<b>-2620</b>	<b>Diff Yrs. 2006-2000:</b>	<b>- 1299 prod.</b>

(Reference: DRA database, 10/2/2006 and Price Lists 2000-2005)

Table 2 indicates the number of authorized products in Cyprus and the number of products actually circulated in the market today (1/4/2007).

TABLE 2:

	Number
Medicinal products with a valid MA:	2694
Medicinal products sold in the private market	2034

Is it reasonable to expect from MAH to repeat the complex regulatory procedures and the costs involved for markets of this size?

## **ESTONIA**

In Estonia the population is 1.3 million. The Estonian medicinal products market was 2.260 billion Estonian kroons (EEK) in 2006 (in wholesaler prices) = 144, 5 million EUR. This includes both, prescription medicines and OTCs. The market increase was 12,4% in comparison to year 2005.

Estonia does not have several important medicinal products, e.g. adrenaline, atropine, calcium gluconate, isoprenaline, phenylephrine, norepinephrine, prednisolon, hydrocortisone, perphenazine, lithium, antituberculous drugs, some vaccines, antidotes in the national register. Several essential medicines have been withdrawn from Estonian market and no alternative is available.

The number of unauthorised medicinal products with patient-based licences is growing every year.

## **FINLAND**

During the last few years Finland has been very popular as a Reference Member State in the MRP procedure. That could, of course, make one think that we would also be the ones to get those products on the market, but that has not been the case. Despite the huge work done for these products by Finland, only a very limited number of the products ever came to our market. As a consequence of this popularity our workload became much too much, and in 2005 we put on our website an announcement where we told the applicants that big delays would be expected, and that from that timepoint on we would give advantage to the products also intended to be marketed in Finland. After this announcement we could see a decrease in the number of applications, but we believe that it was mainly due to the delays, not due to the demand of putting products also on the market in Finland. Some of the applicants now promise to come to the market in order to get their application as first in line, but reality after the approval is different, and we cannot punish them even if we have on paper these promises.

## **FRANCE**

France has given a summary of the French ATU system which was implemented in 1984. This authorisation is called ATU (temporary authorisation of use). It can be used under the condition that first the medicinal product is intended for the treatment of rare or serious diseases, secondly no alternative treatment is authorised in France, and thirdly, data about safety and efficacy of the medicinal product are sufficient to ensure a presumption of efficacy and safety of the medicinal product. There are two types of ATU, on the one hand ATU nominative, granted on a named patient basis after assessment of specific clinical data provided by the ATU applicant, on the other hand the so called cohort ATU which allows a group of patients to be treated with the medicinal product. Recently a law published in February 2007 has extended the scope of the nominative ATU allowing a medicinal product to be subject to the nominative ATU even if the competent authority has only a few documents about efficacy and safety of the medicinal product.

## **ICELAND**

- The population is 0.3 million
- Medicinal Products turnover in 2006 was 19.4 million EUR (2006, retail price VAT included) (IKR 16,4 billion)
- There were 3427 Marketing Authorisations valid on 1 January 2007 of those only 2169 were marketed (63%)

- EU MAs are 941 (27%) and marketed EU MAs are only 349 (37%).
- Icelandic Authority - IMCA received 11.098 applications for MPs on a special license (no valid MA in Iceland). These products are not subject to price control or does it entail responsibilities for the MAH, which means this is a more attractive procedure.

#### Valid MAs in Iceland

	Total	Marketed
DCP/MRP MA	9/586	2/296
EU MA	1016	363
National MA	1614	1403

For some essential active substances there is only one product with a MA on the market. Sometimes such products are not available for some reason, which causes problems. Some examples of MPs without MA in Iceland would be adrenalin, atropine, noradrenalin injections, dexamethason and betametason tablets and betametason injection, ranitidine mixture, sodium bicarbonate infusion, ampicillin injection, some vaccines and antidotes. Parallel Imported medicinal products do sometime cause an availability problem since their stock is not continuous and the wholesaler for the competing product is not prepared for a shortage.

#### **IRELAND**

The Irish Health Ministry has indicated the following important perspectives and issues concerning the availability of medicinal products.

1. Particularly interested in what potential (present and future) article 126a has for solving the immediate problem and in hearing the experience of other countries that have used it.
2. Different interpretations of technical data in dossiers.
3. Differences in vaccine schedules/ policies and labelling and pack size requirements between neighbouring countries with similar language, can also go against the smaller countries when it comes to obtaining supplies/attracting tender offers.
4. Large countries that purchase under contract and have penalty clauses tend in times of shortages, to get delivered product by suppliers in preference to smaller countries. Even if smaller countries include penalty clauses, the larger country may be given preferential treatment.
5. Non availability of NPARS.
6. Coordinating processing of variation applications across countries.
7. Distribution Difficulties.
8. Cumbersome pricing and reimbursement arrangements.
9. Poor price transparency or restrictive pricing practices.
10. Mergers and Acquisitions.
11. Implications of Sunset Clause.
12. Tendering/ touting for suppliers of licensed medicines in short supply in small markets - amalgamated European list.

#### **LATVIA**

The population of Latvia is 2.3 million. The first big changes in the drug market took place in 2004 due to accession to the European Union. Latvia didn't have transitional period for MA requirements.

On 1 January 2007 there were 4405 drugs (11621 products) with valid Marketing Authorisation on Latvian market, but only 3609 drugs (5219 products) were marketed

(82%). Correspondingly there were 2503 products with EU Marketing Authorisation, but only 292 (11%) were marketed in Latvia. 118 CA products (52 drugs) and 953 nationally authorised products (also MRP/DCP) (297 drugs) are reimbursed by state.

Parallel import permissions were given for 46 products, but only 37 were on the market. Import licences for 679 unauthorised products in Republic of Latvia were issued in 2006.

In year 2006 Latvian medicinal products market was 148,36 million Latvian Lats (in wholesalers prices for pharmacies, hospitals and clinics) = 211,10 million EUR. The market increase was 17,9% in comparison to year 2005.

As it may be seen from the figures given above, drug availability is a problem also in Latvia. The agency is on the position that the cause of this problem to great extent is the drug market of Latvia being comparatively small. The marketing of CA products is especially low, but the agency can not assert that it is directly entailed with these products being included or not in the list of reimbursed medicines.

In each case there are different solutions used to handle the situation. In the most of cases unauthorised products are imported and there are cases when due to economic reasons wholesalers tend to choose the products from third countries. Each of these cases is evaluated separately by the agency.

There is a tendency that companies ask for permission to distribute medicinal products with non corresponding labelling (in other EU language). They substantiate it with insufficient amount of product. This practice predominates with CA products.

Article 5, 81 and 126a of Directive 2001/83/EC are implemented in the national legislation. Till now, no procedure according to Article 126a has been started.

## **MALTA**

The size of population in Malta is 0.4 million. Prior to accession into the EU there were 7020 different medicinal products which could be placed on the market in Malta. Now, there are 2000 national authorisations for medicinal products, 120 of these are authorised through article 126a.

- Lack of inclusion of all relevant Member States by marketing authorisation holders in Mutual Recognition Procedure (MRP)/Decentralised Procedure (DCP). There are a number of MRP/DCP procedures, which involve most Member States with the exception of Malta and possibly one or two other Member States.
- Complete lack of coverage of certain active ingredients and certain products by the list of products with a marketing authorisation.
- Lack of competition on the market in a Member State for a number of products which alternative products with the same active ingredient are available on the market in other Member States. This can affect the prices of medicines on the market.
- In the case of Malta most companies are only represented by agent/wholesaler who may represent a number of companies. Moreover Malta is still being grouped with Middle East office for some companies and this causes problems with shifting from export to EU packs.
- In the following part you can see the list of essential products which were totally out of supply (i.e. not even one alternative with same active ingredient) on the retail market in Malta at some time from January to August 2007 and where sold through the National Health Service. This list shows the true significance of the problem.

Aciclovir suspension	Lithium carbonate 400mg tabs
Acetazolamide 250mg tabs	Loperamide hydrochloride syrup
Adrenaline junior/ adult pen	Magnesium Hydroxide mixture
Alfacalcidol 1mcg tabs	Malathion lotion 0.5%
Amantadine 100mg caps	Medroxyprogesterone depot 150mg
Amiloride 5mg tabs	Menadiol sodium diphosphate (Vit K) 10mg tabs
Amitriptyline 25mg tabs	Mesalazine 500mg supps
Amitriptyline 10mg tabs	Mesalazine 400mg tabs
Amoxycillin injections 500mg/ 250mg	Pyridostigmine 60mg
Amoxicillin 3g sachets	Methotrexate 2.5mg tabs
Amphotericin lozenges	Methyldopa 250mg tabs
Azathioprine 50mg tabs	Metoclopramide 10mg tabs
Baclofen 10mg tabs/syrup	Metolazone 5mg tabs
Beclomethasone 250mcg inhaler	Metoprolol 50mg/100mg tabs
Beclomethasone 50mcg inhaler	Metronidazole supps 500mg
Benzhexol 2mg tabs	Mianserin 10mg/30 mg tabs
Bezafibrate 400mg tabs	Naltrexone 50mg tabs
Budesonide nebuliser solutions	Nicorandil 10mg tabs
Bumetanide 5mg tabs	Nitrofurantoin tabs 50mg
Buspirone 10mg tabs	Nitrofurantoin syrup
Cabergoline 0.5mg tabs	Nystatin syrup/cream
Captopril 25mg/ 50mg tabs	Oestradiol implant 50mg
Carbaryl lotion	Olanzapine 10mg tabs
Carbidopa/ levodopa 110/275mg tabs	Ondansetron 4mg/ 8mg tabs
Chloramphenicol eye ointment	Orphenadrine 50mg tabs
Chloroquine phosphate 250mg tabs	Oral Iron preparation
Chlorpromazine 25/100mg tabs	Orciprenaline sulphate syrup
Cholestyramine sachets	Oxybutinin 2.5mg/5mL syrup
Ciprofloxacin syrup	Pancreatin/ Pancreatin forte tabs
Clioquinol 1% & Flumethasone 0.02% ear drops	Phenoxymethylpenicillin 250mg tabs and syrup
Colchicine 500mcg tabs	Phenytoin 50mg/100mg/300mg tabs
Compound alginate sachets (Gaviscon infant)	Potassium chloride mixture
Cyclopentolate drops	Potassium efferverscent tabs
Cyproheptadine 4mg tabs	Prazosin 1mg/2mg tabs
Cyproterone acetate 300mg/3ml depot	Prednisolone 1mg tabs
Dantrolene 25mg tabs	Prednisolone enemas
Dapsone 50mg/100mg tabs	Primidone 250mg tabs
Desmopressin spray/0.1mg tabs	Procyclidine injections
Dexamethasone 0.5mg/2mg tabs	Profasi injections
Diethylstilbestrol 1mg	Promazine 25mg tabs
Diltiazem 60mg tabs	Promethazine injections
Dipyridamole 25mg/100mg tabs	Promethazine syrup
Disopyramide 100mg tabs	Propaferone 150mg tabs
Disulfiram 200mg tabs	Propylthiouracil tabs
Enoxaparin injectios 40mg, 100mg	Quinine sulphate 300mg tabs

Erythromycin 250mg tabs and syrup	Ranitidine syrup
Etanercept injections	Rifampicin 300mg & Isoniazid 150mg tabs
Ethinylestradiol tabs	Salbutamol respirator solution
Ethosuximide tabs and syrup	Synthrtic Salmon calcitonin injections
Fenofibrate 100mg/300mg tabs	Selegiline 5mg tabs
Flavoxate Hydrochloride 200mg tabs	Sodium bicarbonate tabs
Fludrocortisone 0.1mg tabs	Sodium fusidate syrup and tabs 250mg
Fludrocortolone 20mg	Sotalol 80mg tabs
Flupentixol 20mg injections	Spironolactone 25mg
Fluphenazine 25mg/100mg inj	Stilboestrol 1mg tabs
Folic acid syrup	Sucralfate 1g tabs/ syrup
Gabapentin 100mg/300 mg tabs	Sulphasalazine tabs/syrup/supps
Gentamicin 80mg injections (require doctor/ consultant's note)	Sulphinpyrazone 200mg tabs
Gliclazide 80mg tabs	Sulpiride 50mg caps/200mg tabs
Glyceryl trinitrate 500mcg sublingual tabs	Testosterone 100mg injections
Griseofulvin 125mg tabs	Testosterone 250mg inj
Haloperidol 0.5mg/1.5mg/5 mg tabs and syrup	Testosterone 40mg caps
Haloperidol 50mg/100mg depot injection	Testosterone 100mg implant
Heparin calcium (Calciparine) injections	Tetrabenazine 25mg tabs
Human chorionic gonadotrophin injections 5000 IU	Tetracycline 250mg tabs
Hydralazine 25mg tabs	Ticlopidine 250mg tabs
Hydrocortisone 10mg/20mg tabs	Tranexamic acid 500mg tabs
Hydrocortisone foam enemas	Triamcinolone acetonide 40mg inj
Hydroxocobalamin (Vit B12) 1mg injections	Trimethoprim tabs and syrup
Hydroxyurea 500mg caps	Trimipramine 25/50mg tabs
Imipramine 10mg tabs	Ursodeoxycholic acid caps 250mg
Indomethacin 100mg supps	Vigabatrin sachets
Indomethacin 25mg caps	Vallergan forte syrup
Isosorbide dinitrate 10mg tabs	Verapamil 40mg tabs
Ketoconazole 200mg tabs	Warfarin 1mg
Labetolol 100mg/200mg tabs	Zuclopentixol injections and tabs 10mg
Liothyronine 20mcg tabs	

## THE NETHERLANDS

### Policy on availability of medicinal products in general

The Minister of Health, Welfare and Sports is responsible for the availability of human medicinal products in the Netherlands. This responsibility is laid down in the Medicines Act, the Health Insurance Act and several acts concerning pricing and reimbursement of medicinal products. The Medicines Evaluation Board (MEB) and the Netherlands Health Care Inspectorate are responsible for the implementation of the policy with respect to the availability of Medicines. The Health Care Insurance Board co-ordinates the implementation and funding of the Cure Insurance Act and the Exceptional Medical Expenses Act.

## **The Medicines Evaluation Board**

The MEB is the executive body, which approves or rejects Market Authorisation Applications for medicinal products in the Netherlands. On 1 January 2007 12.256 Market Authorisations were recorded in the registry of the Medicines Evaluation Board. In our report on the situation in the Netherlands the focus is on the non availability of medicines caused by the decision of the company not to apply for MA or it is nationally registered, but not available on the market ('constant' is the classification use by the taskforce).

The Dutch Medicines Act contains an article concerning the Sunset Clause. The MA of a medicinal product will be withdrawn when a pharmaceutical company has not to market for more then 3 years a registered medicinal product. In the sense of medicinal product in all its forms and strengths, for example if only one type of tablet is available on the market the 'whole range' falls without the scope of the Sunset Clause. The company has to market at least one product in order to avoid application of the Sunset Clause. These medicinal products are registered in the internal database of the MEB and each Marketing Authorisation holder has to pay a fee à € 980 for every year to be registered.

There is no legal requirement for companies to produce medicinal products. However, pharmaceutical companies are required by law to fill in a withdrawal form when they want to withdraw from the Dutch market. This form can be found on the website of the MEB: <http://www.cbg-meb.nl/uk/reghoudr/index.htm>.

The market authorisation holders have to inform the MEB, whether:

- there is a product with a similar therapeutic mechanism available on the Dutch market;
- there is a similar product available on the European market.

Subsequently, MEB members of the Board are consulted because of their specialities and they are able to assess the impact of the withdrawal. It is, however, the company that refers to an alternative therapeutic mechanism. Most of the times the employed definition is rather broad and alternatives are not applicable for all type of patients. For example, in some cases there's not an alternative for children or patients that have difficulties swallowing.

- The outcome of the consultation and the withdrawal form are discussed in an internal working group, which is chaired by the chairman of the MEB. This deliberation can either result in the acceptance of the withdrawal of the MA or the request of withdrawal will be upheld. The case-manager of the MEB will contact the pharmaceutical company, whether it is possible to keep the drug in production. If not, the outcome of the deliberations with the pharmaceutical company could result in the transfer of the market authorisation to another company.

## **Registration phases**

### **1) Pre-registration phase**

If a medicine is still in a pre-registration phase a company can decide to make the drug available via the compassionate use programme (article 83 Regulation 726/2004). With the introduction of the Dutch Medicines Act it became a task of the MEB. Companies have to pay the fee à € 3.300 for medicinal products if it concerns compassionate use if the research protocol is ended. It becomes difficult is when a trail started initially on named-patient base, but falls with the introduction of the new law under compassionate use. This question was raised during the distribution of one antiretroviral medicinal product. Some patients were treated on patient named basis. However, the supply is

rapidly decreasing and the firm wants to start a new trial. For every first delivery to a patient or for the import a GP had to sign a Patient Informed Consent Form.

## **2) Post- registration phase**

### **Withdrawal because of economic motives**

There is a distinction between withdrawal due to safety reasons or of economic motives which both can lead to shortfall of stock. In case of safety reasons one could think of the withdrawal of mexiltine in case of recessive myotonia congenital (Becker-type myotonia) or in case of batches for vaccins. The focus in this paper is however on economic motives to withdraw and are illustrated by some examples. The MEB was f.i. informed by mail that the registration of pancreatic enzyme capsules will end 31st December 2007 and confirm that the stock will be finish mid 2008. The firm already informed health professionals and admits that there can be a problem with the treatment of children. The MAH proposes that patients should switch in time to other medication.

Another example is the drug Monoflor (for the treatment of otosclerose) where the firm explicitly stated that the use of 18 packages in 3 year was economically not in line with the cost of registration, updating the dossier etc. Or the withdrawal of a antispasmodic suspension for oral use and only tablets or capsules of the same product remain available on the national market.

### **Non-registered circumstances or non availability after a withdrawal**

#### **a) Import from other countries**

If a pharmaceutical company decide not extend their registration (whether it is a national or centralised registration) there is the possibility of ‘transferring’ their market authorisation to another national company. However if this is not an option there are in case of a centralised procedure, but no available on the national market, several options:

- In case a drug is not registered in the Netherlands (by the national procedure) it can be imported
- In case of registered drug by the centralised procedure, but not on the market in the Netherlands, a GP can request to prescribe a drug on a named patient basis. This means that the medicinal product has a designated recipient. The Netherlands Health Care Inspectorate (IGZ) has to approve the import and the GP is responsible for the information (translation of the leaflet i.e.) to the patient. The difficulty here lies for the Inspection in the available of information of the drugs in other countries. If there is no information in Dutch available the MEB could allow a simplification of the labelling requirement. For example in case of a centralised procedure the packaging and/or instruction leaflet could be delivered (via the EMEA database) on an ad hoc basis printed in Dutch.
- Another solution could be that a hospital pharmacy or commercial companies imports a registered drug. A GP has to give permission if it is not registered (in the case it concerns compassionate use). When the drug is registered in the Netherlands but not available the Netherlands Health Care Inspectorate (IGZ) has to approve the import (in the form of a permit in the form of a GMP-hospital permit).

#### **b) Production of medicines by hospital pharmacies**

If a medicine is not registered (not centralised, nor decentralised or by mutual recognition) hospital pharmacies are allowed to produce and deliver a ‘non-registered’ drug. This type of compassionate use involves the MEB (Board has to give approval of the compassionate use) whereas the Inspection is responsible for the surveillance. However there is a

tendency to produce not only for own patients and the Inspection pushes back this development.

There are approximately 95 hospital pharmacies that can produce medicinal products without a marketing authorisation. These unregistered products are produced on a small scale. This type of custom made drugs are rather costly and without a registration it is more difficult to guarantee patient safety. These pharmacies are required to:

1. argue that there is no similar medicinal product available in the European Union.
2. draw up a dossier (literature study, because there is not a final clinical study) concerning the fabrication of this specific medicinal product which is being evaluate by the Inspection.

Distribution to other pharmacies is not allowed unless another Dutch hospital pharmacy purchases it. The hospital pharmacies have to comply with the GMP norm. The MEB favours restraint with respect to the production of medicinal products by pharmacies.

### c) Production by pharmacies on named basis

A pharmacy can prepare a drug for on an individual level for its own patients.

### Conclusion

- The turnover of medicinal products in the Netherlands was € 4.346.568.000 in 2004 and € 4.523.568.000 in 2005;
- There is relatively low consumption of medicinal products compared to other Western European countries.
- Costs of medicines is 80% of the total healthcare costs.
- Composition of Prescribed Medicines in the Netherlands:

	2000	2001	2002	2003	2004
Trademarked medicinal products	43,1%	42,8%	41,7%	38,9%	38,0%
Parallel import	7,1%	7,1%	6,7%	6,9%	7,4%
Generics	41,5%	42%	43,8%	46,5%	46,6%
Preparation by pharmacists	8,3	8,1	7,8	7,7	8,0

The Royal Dutch Association of Pharmacies (KNMP) has an internet site, which registers the availability and substitution of medicinal products and medicinal substances: <http://farmanco.knmp.nl/>. The KNMP also issued a book on the guidelines with respect to the fabrication of medicinal products. It also provides information on the quality standards, storage conditions and the therapeutic indications of the medicinal product.

The predominant reason for availability problems of active substances is due to economic reasons (this also includes rationalisation of their product catalogue).

These medicinal substances are reported on a voluntary basis by pharmacists, wholesalers, and suppliers and the list is, therefore, incomplete:

- 53 active substances in 2005
- 48 active substances in 2006
- 46 active substances in 2007.

The conclusion is there are 2 directions namely produced by a firm (with the economic motives not to market in a small country) or pharmacies, mostly hospital pharmacies, preparing drug for patients. It is difficult to conclude that non-availability leads to serious health threats, but treatment or prevention of serious conditions can be at risk.

## NORWAY

The sales of medicines amounted to NOK 16.4 billion (PRP) in 2006. Measured as PPP, sales amounted to NOK 10.6 billion. The sales of medicines in terms of defined daily doses (DDD) have increased by 4.1 percent from 2005 to 2006. From 1999 the sales growth in terms of DDD has fluctuated between 8.0 percent and 3.4 percent. Altogether 47 new chemical entities were introduced on the market during 2006. In total 2 551 medicinal products are marketed in Norway, distributed between 1 414 chemical entities. Generics have a 46.2 percent share of the total generics market by value and a 70.8 percent marketshare by volume (DDD). Parallel imported medicines comprise 5.9 percent share of the total market, compared to 6.9 percent the previous year. In 2006, 1 414 active ingredients had a Norwegian marking authorisation. Out of the total 6 829 marketing authorisations in Norway in 2006, 2 515 are nationally granted authorisations, 1 440 authorisations granted through the mutual recognition procedure, and 2 874 through central procedure. Veterinary medicines are included in the figures, while herbal medicinal products, radiopharmaceuticals and parallel imported medicines are excluded.

Countries like Norway are small countries with their own languages (4.6 million inhabitants). Even if one looks at a common Scandinavian market (Scandinavian packages), the markets still are perceived small. In Norway the most usual Scandinavian packages are Swedish/Norwegian, i.e. 2 languages, and compared to larger language markets this is still a limited market. Scandinavian labelling also has as a prerequisite a common interpretation of the rules and regulations and that the PIL is the same in all languages.

An additional reason may be that for prescription medicinal products there is maximum pricing, and a fixed pharmacy gross profit (between 10 to 14%). Medicinal products sold under the exemption to licensing regulation, has no maximum pricing and the pharmacy gross profit is 25%, so it is more attractive for the MAH and the pharmacy that niche products are sold under this scheme.

A very concrete example shows that Dexametasone tablets, Naloxone injections, Ampicillin tablet have been withdrawn from the Norwegian market recently.

Norway has some experience in on publishing stock shortages. The agency has published 12 such notices with recommendations and they have had positive feedback, especially from the pharmacies.

<b>Facts and figures of the pharmaceutical market in Norway (2006).</b>	
No of active substanses on the market	1414
No of new active substances on the market in 2006	47
No of withdrawn active substances in 2006	20
No of product names on the market in 2006	2551
No of MA in 2006	6829
Value of pharmaceutical market in 2007 (VAT included)	16.4 billion NOK
Sales per inhabitant	NOK 3534
New innovative medicines' share of the market	7,40%
Market share of generic medicines	35,40%
Public financing of medicines	70%

## **PORTUGAL**

The agency of Portugal considers the availability of medicinal products to be a serious public health problem in the country. Out of all the medicinal products authorised by the centralised procedure, only one third are currently being marketed. In 2006 the agency had 367 information requests from the general public on medicines shortage and 258 in 2007. INFARMED receives information on availability problems through various channels (but not yet through a centralised information system). Only in 2007, 193 medicines shortages have been notified to INFARMED. In June 2007 the web page has information on 624 shortages (since the start of this project two years ago), of which 289 have been resolved and 334 are still outstanding. In 2006 the agency had 367 information requests from the general public on medicines shortage and 258 in 2007. The follow-up of these requests normally results in contacts with other EU agencies. In these cases INFARMED contacts the wholesalers and the MAH with a view to ensure the re-supply of the market. Sometimes it works, sometimes it does not.

## **SLOVENIA**

In Slovenia a small market is illustrated by the following data:

- The population is 2 million.
- About 3200 products are authorized.
- Value of the pharmaceutical shows relatively high consumption.
- Favorable situation for new products (self-assessment).
- The flexible regulatory system for interventional measures e.g. not high costs for regulatory procedures, multilingual labeling or stickers is used.
- Small number of both pharmaceutical and therapeutic parallels.
- Balanced pricing system (innovative vs. generic products, comparative prices vs. negotiations) (self-assessment)
- About 40% of CP products are available on the market
- The agency considers having problems with availability of MPs.

Authorities are trying to solve the problem by using interventional import of necessary MPs (About 200 import license/year for non authorized products) and by introducing more flexibility into regulatory system within the borders of the acquis

The existing legal background is considered to be insufficient for ensuring availability of medicinal products on small markets. Patients depend on willingness of manufacturers to make their products available.

## **SPAIN**

The Spanish Agency for Medicines and Medical Devices has a great concern about the problems some our patients have to get their treatments due to the non-availability of some medicinal products. Spain is the 5th pharmaceutical market in Europe so the size of the market is not a root cause for this situation.

In the last years the agency has the experience of an increasing number of shortage of some medicines, many of them related to parallel export. Because of these shortages, patients do not find the prescribed medicine and this even leads in some cases to changes of treatment or even treatment interruptions. As the occurrence of these situations is increasing, the problem is becoming a national issue. The Defensor del Pueblo (Spanish Ombudsman), that is the institution acting as the high commissioner of the Parliament at the service of citizens, has recently requested the Spanish health authorities, in the name of patient associations, to implement the necessary measures to solve this problem. A recent

case, related with parallel trade, has been that of Neupro(R) (Rotigotine Transdermal System) for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease. This case motivated a complaint from the Parkinson's patients association. Examples of other cases of special importance because they involve medicinal products with no therapeutic alternative in which the interruption of the treatment may have relevant consequences: imatinib, fludrocortisone, tacrolimus, or piridostigmine.

In other recent cases, not related to parallel market, there has been lack of medicinal products without previous notice by de MAH in spite of being medicines that could not be suddenly stopped: tranylcipromine, primidone, trifluoperazine.

The art 81 of the Directive establishing the obligation of continuous supply, along the supply chain, within the limits of their responsibilities, as it is stated in the article has been transposed into the Spanish law. Transposition of articles 5 and 126a is complete in Spanish regulations.

As described before in Spain parallel export is a main cause of availability problems. The agency is considering the possibility of implementing measures to regulate parallel export so as it would only be possible after being sure that normal demands in the Spanish market are met.

Based on the experience of Spanish agency, the promotion of parallel importation in case of shortages is not a good idea, because it usually will generate shortages in the country of origin.

The agency is also concerned about already marketed medicinal products for life-threatening diseases or other indications in which shortage can cause a risk for patients. A penalty to the MAH is not a real solution for these cases. There should be a special obligation for the MAHs to provide these medicines, a possibility could be the obligation to keep a reserve stock that could be regulated.

## **SWEDEN**

Swedish Agency supports the conclusion that there is a need for a review of the legislation on medicines availability. Shortage due to production problems and MAHs obligations in this respect should be included. The MAH should be responsible for developing crisis management plans for use of alternative medicinal products should their product be unavailable.

SE has not had problems to any extent of unavailability of authorised CAPs and MRs or for parallel export reasons.

### Appendix 3 - Examples from the Member States for solving the availability problems

- Patient or hospital based solutions.
- Several countries have introduced a system which allows the unauthorised medicinal products to be imported and used, on the basis of a single authorisation for import and use of the agency, at the medically justified written request of a doctor or veterinarian qualified to prescribe the medicinal product for the treatment of a person (persons in the hospital) or animal treated by the doctor. The question of dividing the responsibilities and liability in this procedure for damage to health resulting from the use of the medicinal product for its intended purposes between government, agency, physician, hospital or manufacturer have been solved in different ways.
- Special permission in specified situations.
- Some countries have introduced a system which in the absence of an authorised medicinal product with equivalent effect or if such product is not available, allows the agency to grant authorisation to import and use: unauthorised medicinal products based on an application of a professional organisation of doctors for a diagnosis specified in the application; unauthorised antidotes or unauthorised medicinal products for use within the framework of national programmes. In addition some countries may also grant authorisation for the import and use of unauthorised medicinal products for use in special and identified emergencies.
- Licences for parallel import, parallel distribution. It is important to mention here that based on the experience of Spanish Authority they are not in favour of promoting parallel import as the possibility for solving the availability problems, because it usually will generate shortages in the country of origin.
- Fee waivers or fee reductions for national authorisation procedures for low-turnover medicines.
- Financial or other support for research into development of suitable medicinal products.
- Identification of medicines authorised in other MSs and the provision of special import licences for such products.
- Pragmatic use of bi-lateral mutual recognition when needed.
- Pragmatic flexibility to packaging and information in local language requirements when needed.
- The 3 Baltic States are promoting the common Baltic labelling to lower the costs of production. The requirements of patient information and labelling of package are similar in three Baltic States and have been confirmed by the heads of drug regulatory authorities at first in November 1999 and updated in May 26, 2005.
- In Iceland, the PIL in Icelandic language may be printed out only in the pharmacy – no need for the company to add it to the package.
- Lowering of the fees for authorisation of products by MRP or DCP and for authorisation by article 126a.
- Adoption of article 126a of Directive 2001/83 as amended by Directive 2004/27.
- Marketing authorisation holders are being encouraged to include small and economically unattractive countries in MRP/DCP procedures as CMS with other Member States. There is increased direct communication with marketing authorisation holders.
- Marketing authorisation holders are encouraged to produce a joint pack with that supplied in other Member States

- Not setting prices of medicines before they can be placed on the market.
- Some MSs have an especially dedicated website on market shortage indicating the date that the medicine will be on the market again.
- In Norway, the labelling in Norwegian is needed, but harmonisation of PILs and labelling should facilitate Scandinavian packages.
- In Cyprus the labelling, and PIL of medicinal products may be drafted in either the Greek or English language. Country specific information should be present. Labeling and PIL contain country specific information (such as the name and address of the MAH and the number of marketing authorisation). The problem was tried to alleviate by making arrangements with the Greek National Drugs Organisation (EOF) to accept common package with country specific information for both countries.
- Small language area makes production for the market expensive. Several countries (e.g. Norway) have introduced a system for niche products to defer registration fee or yearly gross turnover fee. For products like orphan drugs, the usual pricing rules are waived and they get their proposed price in Norway. So far the pharmaceutical package has not been implemented in the EEA-agreement, but a voluntary warning system for the MAH regarding interruption of delivery to the Norwegian market has been introduced. In case of interrupted delivery, the exemption from the requirements for labelling in Norwegian can be made, and the wholesalers may import foreign packages.
- Malta allows the placing on the market of products, which can only be in the English language.
- The obligation of the MAH and wholesalers has been enforced in Spanish Medicines Law (Law 29/2006) to keep the Spanish market supplied. The regulators in Spain are considering the possibility to draft regulation to intervene in parallel export of specific products in cases there is a situation of national non-availability that implies a public health problem.
- An early warning system has been introduced since January 2007, based on an e-room that provides permanent on-line transmission of these problems when detected by any regional health authority in Spain.
- The agency in Spain has implemented, since March 2007, an information system to which the MAHs and wholesalers send on line information to the health authorities about supplies and returns, in order to identify irregularities and responsibilities (e.g. wholesalers that provoke non availability due to a high parallel export).
- Search of an alternative therapeutic solution under the form of another medicinal product authorised in the country.
- Alternative under the form of a magistral preparation.
- Subcontracting of particular magistral preparations by an authorised person/company.
- Derogation given by the authority to the company, allowing the company to import and market foreign packaging under conditions (i.e. re-labelling of the packaging).
- Import of a medicinal product by the pharmacists, from other countries where the necessary medicinal product is authorised (an import on patient named basis).

#### **Appendix 4 - References**

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## **Appendix 5 – List of members of the Task Force**

Rannveig Gunnarsdóttir	Icelandic Medicines Control Agency
Gro Ramsten Wesenberg	The Norwegian Medicines Agency
Martina Cvelbar	Slovenian Agency for Medicinal Products and Medical Devices
Kristin Raudsepp	Estonian State Agency of Medicines
Panayiota Kokkinou	Ministry of Health Pharmaceutical Services, Cyprus
Patricia Vella Bonanno	Medicines Authority, Malta

## **Appendix 6 - Abbreviations used in the document**

CA	Competent authority
CAP	Centrally Authorised Products
CMD	Co-ordination Group for Mutual-Recognition and Decentralised Procedures
CMS	Concerned Member State
CP	Centralised Procedure
CTS	Communication Tracking System
DCP	Decentralised Procedure
EC	European Commission
EEA	European Economic Area
EEC	European Economic Community
EFTA	European Free Trade Association
EMA	European Medicines Agency
EU	European Union
GMP	Good Manufacturing Practice
HMA	Heads of Medicines Agencies
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MRP	Mutual Recognition Procedure
MS	Member States
QRD	Quality Review of Documents
R&D	Research and Development
RMS	Reference Member State
SPC	Summary of Product Characteristics
TF	Task Force on medicines availability