

Draft common position between patients', consumers, and healthcare professionals' organisations involved in the activities of the European Medicines Agency on:

## Supply Shortages of Medicines

### Acknowledgments

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### Draft common position

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## 1. Introduction

A supply shortage of medicine may be defined as a situation in which the total supply of an authorised medicine or of a medicine used on a compassionate basis is inadequate to meet the current or projected demand at the patient level. The shortage may be local, national, European or international.

This common position prioritises supply shortages that affect medically necessary medicines (also called essential medicines). It proposes solutions on many aspects, acknowledging other issues exist that need further discussions.

W.H.O defines essential medicines as medicines that satisfy the priority health care needs of the population. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality (and at a price the individual and the community can afford).

Regardless of the cause of a medicine shortage, the public health consequences can be severe and cause a ripple effect that disregards national boundaries. The trend is particularly alarming as shortages affect the entire healthcare system, industry, healthcare professionals, and uppermost, the patients.

### 1.1. Extent of the problem

The number of reports of medicine shortages in the EU is increasing. According to these reports all classes of medicines are affected (see annexe 1 for shortages listed by some Member States).

In response to the problem national authorities in a number of EU Member States have started monitoring the situation and have set up websites for the public where information about current shortages is available.

In the UK, the Pharmaceutical Services Negotiating Committee (PSNC) maintains a list of branded medicines in shortage<sup>1</sup> since 2012. This list is derived from information reported by pharmacies to PSNC and contains between 30 and 40 products at any given

<sup>1</sup> Report of the All Party Pharmaceutical Group, Rt Hon Kevin Barron Member of parliament, England and Wales. Inquiry into Medicines Shortages. [Here. http://www.webcitation.org/6Hz6BmqPR](http://www.webcitation.org/6Hz6BmqPR)

time, and they vary over time. The 30 to 40 products reported to be in shortage at any given time compares with circa 16,000 licensed preparations of medicines in the UK. However it would be wrong to conclude that the small percentage reported equates to a minor problem. The small proportion of medicines in shortage causes acute and disproportionate problems and difficulties for pharmacies and for patients.

In France, the National Academy of Pharmacy organised a conference<sup>2</sup> on medicines supply shortages on 20 March 2013. Pharmacists explained that everyday 5% of supply they ordered to wholesalers was out of stock in 2012, and for half of cases the shortage lasted for more than four days.

The evidence of a growing problem of medicine supply shortage in Europe has grown starker in recent years: in a European survey<sup>3</sup> to which over 300 hospital pharmacists from 27 countries responded in 2012, 99% pharmacists reported that they have been experiencing problems with medicines shortages, 63% reported the problem to be a weekly or daily occurrence and 73% said the problem has grown worse in the past year.

Annexe 1 lists some recent examples of supply shortages notified to national authorities in Europe in 2012 or 2013: epinephrine (anaphylactic shock syndrome), encapsulated potassium chloride (hypokalaemia), vecuronium bromide (general anaesthesia), rasagiline (Parkinson disease)...

In the US, 178 shortages were notified in 2010, of which 132 (74%) involved sterile injectable medicines. This represented an increase of 192% since 2005.

### 1.2. Consequences for patients

Patients are at risk of suffering deterioration in their health status if they do not receive the medicine they are prescribed in a timely manner, and can ultimately suffer from serious harm that is avoidable. .

For patients, shortages often translate into lower quality and safety of care, and unnecessary distress.

<sup>2</sup> Médicaments : Ruptures de stocks, ruptures d'approvisionnement, Académie Nationale de Pharmacie, *Séance thématique*, 20 March 2013. <http://www.webcitation.org/6HzB9Ly7T>

<sup>3</sup> <http://www.eahp.eu/practice-and-policy/medicines-shortages>

They also reduce the amount of time various categories of healthcare professionals are able to spend with patients as they are being redeployed out of necessity to manage the shortage. Medicine shortages can trigger delays or discontinuation of both essential and recommended medical procedures and treatments, encourage the omission of medicine doses, increase the risk of surgical interventions and/or operating times and negatively impact on patient recovery periods (shortages of anaesthetics). Moreover, medicines that have become unavailable are often substituted with less effective, inferior or more expensive alternatives (which, depending on the nature of the health system in question, may sometimes not qualify for reimbursement). Unfamiliarity with alternative products can lead to an increased incidence of medication errors and/or adverse reactions, potentially causing fatalities, or worsening patient outcomes.

In the UK, patients' associations and other patients representatives, reported a number of incidents where patients diagnosed with schizophrenia, and other mental health conditions, have not been able to access medication they need in order to stabilise their condition because it has been unavailable. Incidents have also been reported where diabetic patients have suffered hypoglycaemic attacks and have been hospitalised as a result of not being able to obtain the medicines they needed due to shortage<sup>1</sup>. The 2012/13 survey of European hospital pharmacists also reported examples of chemotherapy treatments being interrupted or delayed due to medicines shortages<sup>4</sup>.

Among medicines that were recently in short supply in the EU (see a more comprehensive list in annexe 1), there are indubitable examples that illustrate the harm to patients:

- Supply shortages of antiretroviral treatments in France in 2011<sup>5</sup>: patients had to interrupt

<sup>4</sup> <http://www.eahp.eu/sites/default/files/files/EAHPdeplMedicineHR2f.pdf>

<sup>5</sup> TRT5 observations: <http://www.trt-5.org/article334.html>  
TF1, 27 March 2011: <http://videos.tf1.fr/it-we/penurie-de-tritherapie-les-malades-lancent-un-cri-d-alarme-6330845.html>  
L'Humanité Dimanche, 6 October 2011: [http://www.trt-5.org/IMG/pdf/Humanite\\_dimanche\\_06\\_102011.pdf](http://www.trt-5.org/IMG/pdf/Humanite_dimanche_06_102011.pdf)

treatment up to 3 weeks. The control of HIV virus replication was therefore lifted, with the risk of selecting treatment resistant strains, with dramatic consequences;

- Fabrazyme® shortage<sup>6</sup>: Fabrazyme® is an enzyme replacement therapy to treat Fabry disease, a rare and severe disease. A shortage lasted from 2009 to the end of 2012 and was worldwide. Patients were obliged to reduce the dose, or to switch to an alternative orphan medicine which in turn was not available in sufficient quantities. Although adverse reactions were sometimes difficult to objectify, 12% of patients on a reduced dose had a worsening of the disease, with occurrence of strokes, unbearable pain, weekly Fabry crisis, episodes of collapse, of lost consciousness, or hospitalised for other reasons;
- Cerezyme® shortage: Cerezyme® is an enzyme replacement therapy for the treatment of the visceral symptoms of type 1 and type 3 Gaucher disease. This rare disease presents with hepatosplenomegaly, cytopenia and bone disease. Children can be severely affected. A worldwide shortage lasted from 2009 to the end of 2012, leading to interruptions of treatment and recurrence of disease manifestations in many patients<sup>7</sup>;
- Caelyx® shortage<sup>8</sup>: Caelyx® is indicated for severe diseases such as breast neoplasms, multiple myeloma, ovarian neoplasms or Kaposi sarcoma. Due to shortcomings in quality assurance at the manufacturing site in November 2011, the production of 12 products was interrupted, and as there was no alternative treatment for Caelyx®, the EMA recommended maintaining the product on the market, after assessing the risks. This resulted in shortages in several EU countries from August 2011. The transfer to alternative manufacturing sites has been completed in April 2013.

Le Quotidien du Médecin, 31 October 2011: [http://www.trt-5.org/IMG/pdf/31102011\\_ruptures\\_d\\_ARV\\_quotidien\\_du\\_pharmacien.pdf](http://www.trt-5.org/IMG/pdf/31102011_ruptures_d_ARV_quotidien_du_pharmacien.pdf)

<sup>6</sup> EMA recommendations:

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2010/07/news\\_detail\\_001046.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/07/news_detail_001046.jsp&mid=WC0b01ac058004d5c1)  
Eurordis Q&A on Fabrazyme® and Replagal® shortages : [http://www.eurordis.org/sites/default/files/Q&A\\_cross\\_border\\_care\\_fi nal.pdf](http://www.eurordis.org/sites/default/files/Q&A_cross_border_care_fi nal.pdf)

<sup>7</sup> C.E.M. Hollak, et al., Force Majeure: Therapeutic measures in response to restricted supply of imiglucerase (Cerezyme) for patients with Gaucher disease, Blood Cells Mol. Diseases (2009),

<sup>8</sup> EMA recommendations :

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public\\_health\\_alerts/2012/03/human\\_pha\\_detail\\_000058.jsp&mid=WC0b01ac058001d126](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2012/03/human_pha_detail_000058.jsp&mid=WC0b01ac058001d126)

### 1.3. Consequences for healthcare professionals (treating physicians, pharmacists, nurses)

Healthcare professionals have been confronted with several situations of medicine shortages in the past. Their responsibility is to inform patients on an individual basis about the situation and possible solutions. For instance, alternative treatments can be sought. If these are not available, supportive measures may need to be taken, sometimes with extreme consequences, e.g. splenectomy for a patient with Gaucher disease who cannot be treated with enzyme replacement therapy anymore. The frustration of healthcare professionals can be immense when they see their patients deteriorating in the absence of treatments. This frustration is enhanced when information is lacking and/or there is no transparency about how available inventory can and will be distributed. Of crucial importance to healthcare professionals is adequate and immediate information about the cause and duration of the shortage. Their input should be immediately sought when national or international guidelines for patient management are issued.

For health professionals, concerned about direct impact to their patients, shortages also pose particular capacity and communication challenges. Often staff needs to be reallocated and retrained to engage in crisis management activities. According to the PGEU survey on medicine shortages in 2013<sup>9</sup>, community pharmacists spend 2.5 - 5 hours each week processing information, sourcing medicines which they are not able to order from their usual wholesaler, informing patients and looking for an alternative treatment. This equates to 120-240 hours per pharmacy per year. Time solving problems caused by shortages is time that could be better spent advising and caring for patients.

The lack of information about why a shortage has occurred, and when the situation might be expected to improve, leaves community or hospital pharmacists and other healthcare professionals unable to provide reliable assurance of future supply to a patient or

<sup>9</sup> <http://www.pgeu.eu/en/library/2-position-papers/154-pgeu-statement-on-medicine-shortages-in-european-community-pharmacies.html>

healthcare team members, creating unwelcome uncertainty and anxiety for patients.

The increased number of medicine shortage becomes a real challenge for all healthcare professionals including nurses. For example no supply for an anticancer agent may lead to adverse outcomes in cancer patient<sup>10</sup>.

If a medicine in short supply is replaced with an alternative one, the risk of error increases. An American survey on the effect of oncology medicine shortages in cancer care shows that changes in therapy leading to near-miss errors were reported by 16% of participants, with 6% reporting one or more actual medication errors attributable to a medicine shortage<sup>11</sup>. To avoid potential adverse effects due to medication error, it is important to ensure that necessary information about the reasons, the extent of shortage, the remaining stock and alternative treatment is available to all healthcare professionals. a

### 1.4. Consequences for health care providers

Health system managers are faced with increased costs not only as a result of the diversion of resources in order to manage all aspects of the shortage (including identifying its causes and possible solutions, sourcing alternatives, etc.), but also because certain medicines may need to be purchased at much higher prices from so-called "grey market" sources, which also potentially compromise product quality (e.g., counterfeits). In the EU, medicines shortages might also stimulate an increase in cross-border treatments, which poses further challenges for continuity of care and information sharing.

## 2. Possible causes of shortages

There are a number of reasons why some medicines are sometimes unavailable. The medicines supply chain is highly complex and its efficiency relies on performance of each individual actor of the supply chain including raw material suppliers, manufacturers,

<sup>10</sup> J Pharm Pract. 2013 Jun;26(3):183-91. Clinical dilemmas and a review of strategies to manage drug shortages. Rider AE, Templet DJ, Daley MJ, Shuman C, Smith LV.

<sup>11</sup> Am J Health Syst Pharm. 2013 Apr 1;70(7):609-17. National survey on the effect of oncology drug shortages on cancer care. McBride A, Holle LM, Westendorf C, Sidebottom M, Griffith N, Muller RJ, Hoffman JM.

wholesalers, community pharmacies and intermediaries. If there is a disruption at any point of the supply chain shortages can occur.

Such disruptions can be caused by:

### 2.1. Medical or regulatory causes

- Shifts in demand, resulting from an actual use of the medicine which differs from the company's own estimates (e.g. a paediatric medicine also used in adults);
- In some cases, regulatory changes may impact on supply. For example the Heads of Medicines Agencies has warned that the implementation of the Falsified Medicines Directive may negatively impact the medicines shortage problem by restricting the availability of imported active pharmaceutical ingredients<sup>12</sup>.

### 2.2. Economic causes

- The increasingly globalised nature of pharmaceutical manufacturing, with production concentrated in fewer sites distributed around the world. This tendency can have a severe impact on production capacity when for example, quality issues arise, or where there is difficulty in sourcing raw materials, transport hazards, natural hazards;
- In some cases, pricing strategies may impact on supply by reducing sustainability of supply;
- The lack of priority given to smaller markets by the pharmaceutical industry;
- Economic crisis and health budget control, where speculation encourages wholesalers and importers to purchase a medicine in EU countries where the price is lower and sell in countries where the catalogue price is higher. This then limits the supply in the country where the medicine is imported from;
- Decision of the marketing authorisation holder to withdraw the product from the market, for economic reasons;
- Financial pressure on the pharmaceutical industry: cost-containment measures limit their profits and the demand of their share-holders for dividends pressures management to reduce production costs, often to the detriment of quality and quality control.

<sup>12</sup> <http://www.raps.org/focus-online/news/news-article-view/article/2638/eu-falsified-medicines-directive-could-result-in-drug-shortages.aspx>

### 2.3. Manufacturing causes

- Technical issues during the manufacturing process: for example 80% of antibiotics used in the EU are manufactured outside the EU, often in emerging countries (India, China, Brazil, Mexico) – only the final assembling is done in Europe;
- Contaminations or impurities due to inadequate quality assurance
- Contaminations or impurities despite adequate quality assurance. Some medicinal products are very complex molecules or sophisticated biotech products that are more exposed to such risks.

### 2.4. Causes in relation to the organisation of the pharmaceutical market

- Increase in demand due to another shortage;
- The abolition of public service obligation /minimum national stock keeping requirements in some countries;
- The imposition of fixed quotas of medicines by the pharmaceutical industry, often inaccurately judging the true level of patient needs as well as removal of the traditional role of the full line wholesalers as a result of Direct-To-Patient schemes in some markets;
- Good Manufacturing Practices (GMP) in a global world: increasing issue reports by GMP inspectors, difficulties in ensuring / controlling GMP throughout the world;
- Tendering and procurement (e.g. Lithuania and procurement for HIV antiretroviral treatments: a wholesaler submitted a very low price proposal to win the bid but the company could not find the medicine that cheap).

## 3. Possible measures to prevent and manage supply shortages of medicines in the current regulatory framework

**A** fundamental principle: in developing policies and national laws and strategies, all stakeholders and governments must put patient needs first. These strategies should first and foremost aim to ensure timely and adequate supply of medicines to patients.



### 3.1. EMA reflection on supply shortages

At the European Medicines Agency since 2011, the Committee for Human Medicinal Products (CHMP) has repeatedly discussed problems of continuity of supply caused by manufacturing problems in relation to certain medicinal products<sup>13</sup>.

In November 2012, the EMA released a Reflection Paper on Supply Shortages of Medicines caused by manufacturing/Good Manufacturing Practice Compliance problems. This Reflection Paper summarises the lessons learned from previous crises where “the EMA had a supporting or co-ordinating role, and presents short and mid-term actions that may allow the Network to prevent, mitigate, and manage shortages of important medicinal products”. It discusses the regulators’ dilemma, the impact of globalisation, the industry approach, and presents the current regulatory framework.

Furthermore it proposes short and medium term actions, of which many correspond to recommendations patients’, consumers’ and healthcare professionals’ organisations are proposing here.

### 3.2. Recommendations to EMA

- There should be an European office/unit with dedicated staff to facilitate prevention, resolution of and communication on shortages, informing the public, and providing outreach to healthcare professionals, patients’ organisations and other stakeholders (this office could be supervised by the EMA, for centrally authorised medicines and for other medicines based on certain criteria to be defined. It would operate in close collaboration with national competent authorities);
- EMA should collect and publish data on supply shortages in a public catalogue. We urge European authorities to undertake market research to improve their understanding of the scale of shortages, the causes (parallel trade, quotas and other supply chain responses, or other factors), duration of shortages, regional variations, what make a particular medicine attractive to exporters at a particular time, and impact on patients, pharmacists and others. The requirements of the

2012 FDASIA regulation in the USA, with its provision for mandatory annual reporting by the medicines regulator on the state of the shortages problem and actions necessary to address, might be a useful example to follow in this regard<sup>14</sup>;

- EMA should work with the companies to avoid or minimise the effect of a shortage (e.g. contact other manufacturers to increase production, validate the use of a filter when particles in injecting medicines...);
- Good Manufacturing Practices (GMP) inspections by the EMA and national agencies are already conducted on a large scale, however more resources may be needed to conduct inspections worldwide as needed;
- Transparency on inspection reports and instances of non-compliance should be improved (measures decided, timetables, and follow-up). All information on the causes of a shortage should be verifiable by regulatory inspectors, be they the result of a defect, a contamination, delays in the construction of a manufacturing site, difficulties in finding raw materials, consequences of a natural catastrophe, etc. EMA should also monitor the end of the shortage: the plan for managing growth in product demand going forward post-launch should be discussed with all stakeholders. This plan should be validated by authorities, and supervised by inspectors. This will help ensure that patients are not subject to aggressive competition between different pharmaceutical companies for example, where an alternative regimen has been proposed to replace that affected by the shortage. Here again, the interests of the patient should prevail.

### 3.3. Recommendations to public authorities

- To explore *establishment of buffer stocks* to be held by wholesalers to give greater flexibility to the supply chain (htt);
- To ensure fair and adequate distribution of the remaining supply: European and, in some cases, international coordination is needed to ensure fair and adequate distribution of remaining supply. In Europe, the allocation of supply to countries should be decided upon and agreed at the European level by the EMA and its scientific committees, with consultation of healthcare

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[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2012/11/WC500135113.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/11/WC500135113.pdf)

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<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentstotheFDCA/FDASIA/ucm313121.htm>

professionals and patients. The decisions made should be legally binding, and the European authority should have a clear legal mandate to decide and to enforce its decisions in Member States. When a Member State decides to stockpile enough supply for their needs, via a “safety supply”, this should be done in coordination with other Member States, to avoid pre-emption by some to the detriment of others;

- To establish a reporting mechanism to allow health care professionals and patients to actively report evidence of a product shortage to the authorities;
- To examine the causes of medicine shortages and formulate recommendations to prevent or alleviate shortages. There appears to be a responsibility gap between regulatory and public authorities in Europe in relation to fully examining causation of shortage and required solutions. The seriousness of the matter must be grasped and acted upon by those whom the public look to address matters of public health concern.

### 3.4. Recommendations to industry

#### ***Before shortage***

- Companies holding authorisations for medically necessary medicines should present a supply shortage risk assessment plan to European /National competent authorities, prior to marketing authorisation. The applicant would explain how the production capacity is planned in order to satisfy the demand (both for pre-marketing authorisation i.e. compassionate use and after marketing authorisation), and what measures the company could take if there is an issue (higher demand than expected, manufacturing defect...);
- This supply shortage risk assessment (SSRAP) plan should be agreed upon with EMA/national authority before MA. Although small starting companies cannot be obliged to have different manufacturing sites, EMA should think of basic requirements to minimise a risk for shortage, including regular inspections and realistic calculations based upon assessment of population, production capacity etc.;
- The SSRAP should contain the following elements:
  - Information about production and distribution should be shared: confidentiality because of business sensitive information should not be accepted. In all cases, the interest of the patient should be prioritised;

- When planning communication on products in development, anticipate the potential consequences on pre-market authorisation demand (compassionate use);
- When planning a compassionate use programme, ensure inclusion criteria strictly match the definition in Regulation (EC) 726/2004 Title V, article 83.2, for a “group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product”. Else, the demand may oversize the manufacturing capacities at a stage when the manufacturer is still preparing the large scale production for future commercial use;
- The gap that exists between the marketing authorisation date and the amount of product available upstream of the authorisation is often shocking in the context of critical illness and major therapeutic hopes. Industry should adapt its production capacity to the planned dates of marketing authorisation in the US, EU, and Japan, and should master the adjustment of supply according to the patients who need the product the most in an ethical way.

#### ***During shortage***

- The manufacturer/MAA/MAH should inform the EMA and relevant HCP and patients’ organisations as soon as a shortage becomes possible (even if this may create false alerts), in particular for products when a shortage can provoke severe damage to public health, as anticipation is key to prevent damage to the patients;
- When a shortage occurs, the marketing authorisation applicant (MAA) or holder (MAH) should always communicate the exact figures on manufacturing capacities and provide a calendar of production for the weeks/months to come, until the expected end of the shortage. In addition, the MAA/MAH should provide precise figures on how the product is currently used (which quantities are allocated to clinical trials in progress/to start, compassionate use, validation batches, stock for future market launch etc.). This information should be regularly updated and provided to all parties;
- HCP and patients’ organisations should be involved from the beginning and their expertise used to issue guidelines with the aim to protect the most vulnerable patients throughout the EU;

- Transparency is needed with respect to available inventory and a distribution plan should be made in line with recommendations, again involving HCP's and patients.

### 3.5. Other recommendations

- Alternative unlicensed treatments should be made available through compassionate use programmes if considered sufficiently safe;
- General guidelines might be helpful, and should be developed with support of ethicists and legal advisors on how to distribute a small inventory of medicine when prioritisation is impossible (i.e. all patients are in equal need of treatment). Who is responsible to make a choice? How can a choice be made?
- The scope of pharmacy practice should be extended when medicines are in short supply, so pharmacists can use their skills to better manage patient care. Where a medicine is not available, an alternative medicine could be supplied following local guidelines and in consultation with a treating physician.
- Management of shortage in situations of extreme shortage: as a last resort, when it is clear that only very limited supply is available, and no clear biomedical criteria for allocation can be defined by consensus, the opinions of ethics committees already published as well as standard practice are in favour of random allocation (drawing lots). This may well be the only non-arbitrary, rational and fair way to allocate a very limited supply when demand largely exceeds supply. There are successful examples of consensus medical criteria (e.g. for Gaucher disease: the Emergency Treatment Program, set up by EWGGD in collaboration with, but independent from, the marketing authorisation holder, was successful in prioritising patients). But when no consensus can be obtained, drawing lots may well be the only rational way to proceed.

## 4. Changes to the regulatory framework that are needed to better prevent and monitor supply shortages

- Legislation should require companies to notify the EMA of shortages even when the shortage is still uncertain, and not wait for it to be confirmed. False warnings will occur which should be handled with care to avoid unnecessary anxiety;

- Involvement of relevant patients' and healthcare professionals' organisations from the drafting of the SSRAP to until the end of a shortage should be systematic;
- Article 81 of the EU Directive on Medicines for Human Use<sup>11</sup> was intended to ensure adequate supply of any given product to the market. However, there is extensive evidence of situations where pharmacies can't obtain the medicines that they need for their patients. Consideration should be given to strengthening the provisions of Article 81;
- GMP Inspections should be more frequent for all medicines that are placed on the European market;
- For medicines that are life-saving, or to treat severe conditions, with no substitution product, the marketing authorisation applicant should take measures to minimise the risks (no single manufacturing chain, documenting the capacity to satisfy the potential demand for compassionate use and at the time of marketing authorisation...);
- Proposals for the organisation of the European medicine market, pricing policy, differential pricing, parallel import, to prevent "siphoning" supply from one Member State to others. The Commission and Council of Ministers should engage in a full review of the operation of the pricing system in Europe and whether it is best ensuring access to medicines for European patients in the overall sense, including, but not restricted to, its impact on medicines shortages.

However, nothing in the recommendations on supply shortages prevents a Member State from authorising the export of medicines to other Member States to the detriment of patients living on its territory, for instance by siphoning the medicine supply available for treatment of its patients. Export of medicine supply may create a shortage in a Member State for a given treatment. In such exceptional cases, the Member State should retain the right to remedy the situation on the grounds of public health, in accordance with Articles 52 and 62 TFEU. However, this limitation should be without prejudice to Member States' obligations under Regulation (EC) No 883/2004 of the European Parliament and of the Council of 29 April 2004 on the coordination of social security systems<sup>15</sup>;

<sup>15</sup> OJ L 166, 30.4.2004, p. 1.



- Regulatory impact assessments for pharmaceutical related legislation should explicitly give consideration to any potential unintended impacts of a proposed regulation on the medicines shortage problem. For example, the envisaged

difficulties in relation to medicines shortages and the Falsified Medicines Directives provisions on third country API import might have been picked up and managed at an early stage in this case.

## 5. Signatories of the position

Drafting group, alphabetical order:

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Signatories:

To be completed: EMA eligible organisations (patients, consumers, and healthcare professionals).

## Annexe 1: shortages notified in 2012 and 2013

*(The examples below are mentioned for information, and to illustrate different Member States release different information on supply shortages to the public. Similar lists exist in other Member States. In each Member States, the list is not exhaustive, in the absence of depositories of all shortages. Some may now be resumed. For some products, alternative products exist)*

### United Kingdom

Active substance name	Indications or class
Irbesartan	Hypertension
Rasagiline	Parkinson Disease
Brinzolamide	Glaucoma, Open-Angle Ocular Hypertension
Tadalafil	Erectile Dysfunction
Escitalopram	Depression
irbesartan / hydrochlorothiazide	Hypertension
dorzolamide hydrochloride-timolol maleate	ophthalmic solution
Duloxetine	Anxiety or Depressive Disorder, Major Diabetic Neuropathies
travoprost / timolol	Glaucoma, Open-Angle Ocular Hypertension
darifenacin hydrobromide	Urinary Bladder, Overactive Urinary Incontinence, Urge
vildagliptin / metformin hydrochloride	Diabetes Mellitus, Type 2
amlodipine / valsartan	Hypertension
Deferasirox	Iron Overload beta-Thalassemia
Ezetimibe	Hypercholesterolemia
azelaic acid	Mild to moderate rosacea (acne)
Imatinib	Dermato-fibrosarcoma Gastrointestinal Stromal Tumours Hypereosinophilic Syndrome Leukaemia, Myelogenous, Chronic, BCR-ABL Positive Myelodysplastic-Myeloproliferative Diseases Precursor Cell Lymphoblastic Leukaemia-Lymphoma
insulin glargine	diabetes in patients aged two years or older
Telmisartan	Hypertension
telmisartan / hydrochlorothiazide	Hypertension
mycophenolic acid	Prevention of organ rejection after kidney transplants
nystatin	Fungal infections
pipotiazine	Psychotic illness
aldesleukin	Metastatic melanoma
octreotide acetate	Acromegaly; Carcinoid and/or Vasoactive Intestinal Tumours
prednisolone caproate	Haemorrhoids
Montelukast	Prevention and long-term treatment of asthma
tiotropium	Chronic obstructive airways disease
nilotinib	Leukaemia, Myelogenous, Chronic, BCR-ABL Positive
timolol maleate	ophthalmic solution
nebuliser to be used with tobramycin	Cystic Fibrosis Respiratory Tract Infections
travoprost	Glaucoma, Open-Angle Ocular Hypertension
laropiprant / nicotinic acid	Dyslipidaemias

Source: Pharmaceutical Services Negotiating Committee

[http://www.psn.org.uk/pages/problem\\_medicines\\_list.html](http://www.psn.org.uk/pages/problem_medicines_list.html)







## France

Active substance name	Indications or class
atropine eye drops 0.3%	Uveitis in children
budesonide	Crohn's disease, chronic diarrhoea
mecasermin	severe primary insulin-like growth factor-1 deficiency
cefixime	Antibiotic (bronchitis, pneumopathy, urinary infections...)
cytarabine liposome	intrathecal treatment of lymphomatous meningitis
altretamine	Ovarian cancer and bronchial small cells cancer
quinagolide	Hyperprolactinemia
penfluridol	Chronic psychotic syndromes
benzyl benzoate	Scabies, pediculosis
alitretinoine	AIDS related Kaposi sarcoma
amoxicilline	Antibiotic, large spectrum
immucyst	primary or recurrent carcinoma in situ of the urinary bladder
asenapin	Bipolar disorders
carbimazole	Hyperthyroidism
verapamil	Paroxystic tachycardia, ventricular rhythm disorders
tetracosactide	West syndrome
imipramine	Severe depression, bedwetting, neuropathic pain in adults
encapsulated potassium chloride	Hypokalaemia
vecuronium bromide	Used for general anaesthesia
prednisolone acetate	Local corticoid
hydroquinidine	Ventricular rhythm disorders
inactivated Salmonella typhi bacteria	Typhoid Vaccine
betamethasone disodium phosphate	General corticoid treatment
cidofovir anhydre	AIDS related cytomegalovirus retinitis
fomepizole sulphate	Acute intoxication by ethylene glycol or methanol
mitomycine C	Urinary bladder cancer
Voriconazole	Antifungi large spectrum
netilmicine sulphate	Antibiotic, large spectrum
mitomycine C	Stomacal, pancreatic, rectal, large intestine or kidney adenocarcinoma and their metastases
ganirelix acetate	Used for medically assisted procreation
hydroxocobalamine acetate	Biermer disease, total gastrectomia, Imerslund disease
Gentamicin	Antibiotic
Epinephrine	Anaphylactic chock
peg-interferon alfa-2a	Hepatitis B or C chronic infection
ethambutol chlorhydrate	Tuberculosis infection
Levothyroxine	Hypothyroidism
Iproniazide	Depression









Source: Agence Nationale de Sécurité du Médicament et des Produits de Santé













[www.ansm.sante.fr](http://www.ansm.sante.fr)

Netherlands 12 July 2013

Type	Active substance	Brand	Form of administration	Revision Date	Impact
	<u>Varicella Vaccine</u>	<u>VARIVAX</u>	<u>Powder for suspension for injection</u>	<u>17-06-2013</u>	<b>Alternatives are not available</b>
	<u>Cefotaxime</u>	<u>Cefotaxime</u>	<u>powder injection</u>	<u>14-06-2013</u>	<u>Import possible</u>
	<u>Typhoid Vaccine, parenteral and oral</u>	<u>Typherix, Typhim Vi, Vivotif</u>	<u>injection, gastro-resistant capsule</u>	<u>08-07-2013</u>	<u>Import possible</u>
	<u>Vinblastine</u>	<u>Vinblastine</u>	<u>Liquid Injection</u>	<u>08-07-2013</u>	<u>Import possible</u>
	<u>Vincristine</u>	<u>Vincristine</u>	<u>Liquid Injection</u>	<u>08-07-2013</u>	<u>Import possible</u>
	<u>Bleomycin</u>	<u>Bleomycin</u>	<u>powder for solution for injection</u>	<u>10/06/2013</u>	<u>Import possible</u>

## Latest Reports

Type	Active substance	Brand	Form of administration	Revision Date	Impact
	<u>Corifollitropin alfa</u>	<u>Elonva</u>	<u>Liquid Injection</u>	<u>08-07-2013</u>	<b>Substitution is possible</b>
	<u>Levothyroxine (sodium)</u>	<u>Euthyrox 75 mcg</u>	<u>tablet</u>	<u>08-07-2013</u>	<b>Solved</b>
	<u>Alendroninezuur colecalciferol</u>	<u>Fosavance 70/5600</u>	<u>tablet</u>	<u>08-07-2013</u>	<b>Solved</b>
	<u>Epirubicin</u>	<u>Epirubicin PCH</u>	<u>infusion, injection</u>	<u>09-07-2013</u>	<b>Substitution is possible</b>
	<u>Lactulose</u>	<u>Lactulose PCH, RP</u>	<u>syrup, powder for oral use</u>	<u>09-07-2013</u>	<b>Substitution is possible</b>
	<u>Enalapril</u>	<u>Enalapril PCH, Apotex, CF</u>	<u>tablet</u>	<u>09-07-2013</u>	<b>Substitution is possible</b>
	<u>Isosorbide dinitrate</u>	<u>Isordil Titradose</u>	<u>tablet</u>	<u>09-07-2013</u>	<b>Substitution is possible</b>
	<u>Ascorbic acid</u>	<u>250 and 500 mg ascorbic</u>	<u>tablet</u>	<u>10-07-</u>	<b>Substitution</b>

Type	Active substance	Brand	Form of administration	Revision Date	Impact
		<u>acid</u>		<u>2013</u>	<u>is possible</u>
	<u>Methylthionine</u>	<u>Methylthioninii chloridum</u>		<u>10-07-2013</u>	<u>Substitution is possible</u>
	<u>Hydrocortison Oxytetracycline Polymyxine B</u>	<u>Terracortril + Polymyxin B</u>	<u>oorzalf</u>	<u>10-07-2013</u>	<u>Substitution is possible</u>
	<u>Hydrocortison Oxytetracycline Polymyxine b</u>	<u>Terra cortril + Polymyxin B Ear Drops</u>	<u>ear drops</u>	<u>10-07-2013</u>	<u>Solved</u>
	<u>Trihexyphenidyl</u>	<u>Artane 2 mg</u>	<u>Tablet</u>	<u>10-07-2013</u>	<u>Substitution is possible</u>
	<u>Bisoprolol</u>	<u>Bisoprolol Teva and Mylan</u>	<u>tablet</u>	<u>10-07-2013</u>	<u>Substitution is possible</u>
	<u>Lamotrigine</u>	<u>Lamotrigine</u>	<u>dispersible tablet</u>	<u>10-07-2013</u>	<u>Substitution is possible</u>
	<u>Methysergide</u>	<u>Deseril</u>	<u>Tablet</u>	<u>11-07-2013</u>	<u>Alternatives available</u>
	<u>Norgestimate / ethinyl estradiol</u>	<u>Cilest</u>	<u>tablet</u>	<u>12-07-2013</u>	<u>Alternatives available</u>
	<u>Atorvastatin</u>	<u>Atorvastatin Pfizer</u>	<u>tablet</u>	<u>12-07-2013</u>	<u>Substitution is possible</u>
	<u>Tropisetron</u>	<u>Novaban</u>	<u>injection liquid, capsule</u>	<u>12-07-2013</u>	<u>Alternatives available</u>
	<u>Tick-borne encephalitis vaccine</u>	<u>FSME immun</u>	<u>suspension for injection</u>	<u>12-07-2013</u>	<u>Solved</u>
	<u>Sucralfate</u>	<u>Sucralfate</u>	<u>tablet</u>	<u>12-07-2013</u>	<u>Substitution is possible</u>

Source: <http://farmanco.knmp.nl/>