Report by the Working Party Drug Shortages

Final report, March 2017

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INTRODUCTION

Working party on drug shortages

The working party on medicinal product shortages was established in late 2013. The Thyrax use case reinvigorated the working group in early 2016. The working group met almost monthly in order to elaborate twenty potential measures. The potential measures have been formulated in order to prevent medicinal product shortages and, should they occur, to address them as fully as possible. Manufacturers, (hospital) pharmacists, health insurers, wholesale suppliers, medical specialists, patients, MEB, IGZ and the Ministry of Health, Welfare and Sport are represented in the working party (see appendix 1 for a list of members). The House of Representatives of the Netherlands was informed of the working party’s progress twice during the course of this process.

The working party based its approach on the principle that solutions to shortages should be addressed within the actor in question’s own sector wherever possible. Agreements were made where required, and changes to legislation are being examined in a number of cases.

The working group’s questions were based on the lessons learned from the Thyrax use case. The issues were timeliness of communication with parties outside of the government, such as pharmacists and patient associations, clear insight into the problem, and clarity about which party was responsible for what.

These lessons were taken into consideration in the creation of the so-called roadmap, which describes various potential solutions and points for attention regarding the notification point’s communication with the field (see report section: Addressing).

Joint Notification Centre

The Medicine Shortages and Defects Notification Centre was established on 1 January 2017. This is a joint Notification Centre for MEB and IGZ, and can be reached via the website www.meldpuntgeneesmiddelenkortendefecten.nl. Marketing authorisation holders and manufacturers must report situations that may result in a shortage using a standardised form. The joint Notification Centre is an important step towards gaining better insight into the causes of shortages and formulating a coordinated approach to preventing and addressing shortages.

Previously, there were two Notification Centres where marketing authorisation holders and manufacturers were required to submit such notifications. Expected shortages were reported to the MEB and unexpected shortages to the IGZ. This resulted in a confusing situation for reporting parties, resulting in failure to submit notifications or submissions to the wrong centre. Previously, there was some confusion about under what conditions a (temporary) interruption of placing a medicinal product on the market needed to be reported. The joint Notification Centre has clarified the issue (see next paragraph).

An operational team, initially consisting of government bodies MEB and IGZ (the Ministry of Health, Welfare and Sport is kept informed) monitors the notifications submitted to the Notification Centre. First, the notification is analysed. Important questions include: ‘What is the medicinal product’s market share?’, ‘Are there alternatives in the market?’, ‘How big is the patient group?’. Following analysis, the operational team determines the route to follow or routes to investigate. A roadmap describing the potential solutions is used. When who is informed and involved in the process is described per route. Coordination of communications is handled by MEB/IGZ, who may delegate (parts of) this task to parties represented in the working party. The roadmap is enclosed (see appendix 2). The roadmap contributes to transparency and predictability of action in the event of a notification.

A notification submitted to the Notification Centre ensures the situation is identified early. This provides time to address it. A delivery problem for a single source medicinal product may require switching to a different active substance. Sufficient time to coordinate with prescribers and
Pharmacists is essential in this case. For *multisource* medicinal products, chances are good a switch will need to be made to a product by another manufacturer containing the same active substance with the same strength. The MEB and IGZ procedure provides for the party with delivery problems to seek out an alternative itself.

Manufacturers / suppliers consider the MEB and IGZ procedure, introduced jointly on 1 January 2017 in order to report shortages and delivery problems, to be a good method to detect any potential shortages early on. An early warning will allow relevant parties to deliberate on adequate measures for preventing negative effects for patients to the greatest degree possible at an early stage. Manufacturers and suppliers will therefore fully cooperate with this procedure. A timely notification is mandatory.

Notifications submitted by pharmacists are not taken under consideration - except those related to manufacturing defects. Pharmacists can submit notifications to KNMP Farmanco. Pharmacists (and parts of the public) are informed about solutions for difficulties with medicinal product availability via Farmanco. Notifications from pharmacists may be passed along the chain - via the wholesale supplier and the manufacturer - and eventually result in submission of a notification to the MEB and IGZ Notification Centre.

The Notification Centre does not apply a definition of a shortage, but describes 'situations' that must be reported. After all, it is unclear whether or not a shortage will develop at the time of notification, or whether a shortage can be prevented or addressed in such a way that the patient will not be affected (greatly). The latter is true of most notifications. Not all delivery problems result in medicinal product shortages for the patient, although the patient may experience some inconvenience. The definition used by the Notification Centre describes situations that may potentially result in a shortage. Therefore, the joint MEB and IGZ Notification Centre views matters from the perspective of the marketing authorisation holder where notifications of medicinal product shortages by marketing authorisation holders are concerned. If a marketing authorisation holder temporarily discontinues a medicinal product, but there are sufficient stocks of the own product on the market, with wholesale suppliers and pharmacies, such that the interruption does not result in shortages, no notification is required. Thus, if a marketing authorisation holder temporarily discontinues a medicinal product, and there are insufficient stocks of the own product on the market, with wholesale suppliers and pharmacies to ensure the interruption does not result in shortages, the joint Medication shortages and defects Notification Centre must be notified. This definition automatically entails that notification of permanent discontinuation of a medicinal product is always mandatory. This is a notification within the meaning of section 49, subsection 7 of the Medicines Act.

The MEB will be implementing major corrective measures in order to obtain a clear picture of which medicinal products are/are not available on the market for medicinal products for which this situation has not changed after 1 January 2017. A separate plan will be drafted for this purpose. For example, the Netherlands may be used as a reference member state in a mutual recognition procedure or a decentralised procedure for technical regulatory reasons, without the marketing authorisation holder having the intention to market the medicinal product in the Netherlands.

If a marketing authorisation holder has an inadequate supply of his own product, and estimates sufficient amounts of alternative medicinal products are available in the market and thus does not expect there will be any problems in the market, this is a 'brief notification' and does not require the entire notification form to be filled out. However, should multiple pharmaceutical companies submit a notification for the same medicinal product, the Notification Centre can take action. MEB/IGZ will follow the usual procedure of analysing the notifications and determining the route to

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1 There are two terms used within the context of medicinal product shortages in German speaking areas: Lieferengpässe bei Arzneimittel und Vorsorgungspässe für Patientinnen und Patienten. problems and ‘care’ problems. Delivery Not all supply problems result in problems for the patient. In both Dutch and English, the term ‘medicinal product shortages’ refers to both delivery and ‘care’ problems.
follow. If the marketing authorisation holder does not have a clear overview of competitors’ market situation, a full notification will be submitted.

The Notification Centre must also be notified of a quality defect in a medicinal product that results in a shortage. The marketing authorisation holder shall also need to estimate his own supply position and, if possible, that of his competitors, as per usual.

The marketing authorisation holder may also submit a notification that smaller or insufficient quantities of the medicinal product will be marketed (e.g. due to increased demand because a competitor is no longer supplying the medicinal product), such that it is expected stock will be insufficient for meeting market demand. This is not a notification within the meaning of section 49 subsection 7 of the Medicines Act, but is relevant information for preventing medicinal product shortages.

Furthermore, based on section 49, subsection 9 of the Medicines Act, a company has (best effort) commitment to maintain sufficient supplies of its own medicinal product available for wholesale suppliers and pharmacists to be able to serve the needs of patients. This formulation in the law means a timely notification, though not included in the Notification Centre’s definition, is mandatory.

Marketing authorisation holders only submit a notification at the level of the pharmaceutical form and strength (RVG number). They do not need to submit a notification if only one (or some) of the pack types/pack sizes in a group with the same pharmaceutical form and strength are affected, as the patient may then be supplied with a different pack size, keeping the medicinal product available. A secondary, practical reason for this is also that various pack sizes fall under the same RVG number. (So if a company has marketing authorization for 5, 10 and 20mg strengths, and the shortage only affects the 5mg strength, the company does have to submit a notification. If the company has marketing authorisation for the 5mg strength in different pack sizes and one pack size is unavailable, this does not need to be reported.)

**Definition of medicinal product shortage**

A medicinal product shortage can be considered from a number of different angles. In addition to the perspective of the reporting party - the manufacturer / marketing authorisation holder - there is also the perspective of the patient who is inconvenienced by the shortage. Most delivery interruptions can be addressed by supplying the patient with a medicinal product with the same active substance with another brand, with the alternative medicinal product already authorised and in stock in the Netherlands. The delivery of medicinal products can be secured in almost all cases.

However, all interruptions to delivery have consequences for the patient, and some have a greater impact than others, and this impact can differ per patient. This also applies to the efforts that pharmacists in particular must make in order to resolve problems due to delivery interruptions, including providing patient support during changes, like other care providers. All parties are aware that all forms of inconvenience should be avoided wherever possible.

The notification point has chosen the following definition of medicinal product shortage, based on a patient perspective: “An interruption of availability of a medicinal product that is a burden for patients and where the burden is greater than is the case for regular (generic) substitution.” MEB/IGZ have therefore decided not to target shortages where an easy switching to the same active substance from a different manufacturer is possible, but to focus their efforts on areas where they can truly provide added value. A shortage where replacement via regular substitution is not simple, for example because control of the patient’s disease requires fine-tuning (as was the case for Thyrax) has the full attention of MEB/IGZ.

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2 In Germany, the following definition of a supply problem has been in use since February 2013 (including the criterion that no delivery can be made for two weeks). „Ein Lieferengpass ist eine über voraussichtlich 2 Wochen hinausgehende Unterbrechung einer Auslieferung im üblichen Umfang oder eine deutlich vermehrte Nachfrage, der nicht angemessen nachgekommen werden kann.”
An answer to the question of how many medicinal product shortages there are depends on the definition of shortage. The Notification Centre opened this year and will inventorise manufacturer notifications, including the causes. Because the Notification Centre has only just opened, no overview is currently available.

Current delivery problems that have been reported to the KNMP by pharmacists are presented on the KNMP Farmanco website (www.farmanco.knmp.nl). The notifications submitted to KNMP Farmanco are verified by the manufacturer. Only delivery problems confirmed by the manufacturer are published. These must involve medicinal products that are available nationally for patients, and a shortage of which is likely to last for more than 14 days. In 2015, there were 625 notifications for the entire year. In 2005 and 2010 there were 179 and 174 notifications, respectively. It should be noted that these figures cannot be verified by other parties.

Out of the sum total of notifications of delivery problems to Farmanco, the most high-impact medicinal product shortages for most parties over the past year were:

- Thyrax (thyroid hormone),
- Carbamazepine (medicinal product for epilepsy),
- Penicillin sodium and benzylpenicillin (for infections of the lungs, airway, throat, middle ear and skin (erysipelas) and Lyme disease, syphilis and meningitis),
- Acyclovir eye ointment (for eye infections caused by herpes simplex virus),
- TetaQuin and VariQuin (plasma medicines for the prevention of various infections, respectively for the prevention of tetanus and chicken pox (varicella zoster)
- Remifentanil (anaesthetic in the hospital).
- Sulfasalazine (medicinal product for severe inflammatory bowel diseases and certain forms of rheumatoid arthritis).
CAUSES OF MEDICINAL PRODUCT SHORTAGES

A number of different causes for medicinal product shortages may be identified. They can be classified into three main groups, namely: manufacturing problems, logistical problems and commercial reasons. Past notifications of shortages made to KNMP Farmanco show that most shortages are due to manufacturing problems and commercial reasons. However, it may be that (some of) the issues that were previously categorised as manufacturing problems are actually distribution problems. The Notification Centre makes this distinction based on consultation with the manufacturers. This will be clarified once analyses of the notifications submitted to the Notification Centre are available.

Manufacturing problems

Manufacturing problems can have a number of different causes. For example, there may be problems with the quality of the medicinal product, for example related to the quantitative (e.g. the amount of active substance is too low) and qualitative composition (e.g. contamination of the product with an additional substance). Additionally, there may be quality defects affecting one of the raw materials (e.g. the active substance is contaminated) or the end product (e.g. the tablet does not dissolve quickly enough). Finally, there may be insufficient compliance with Good Manufacturing Practice (GMP) or Good Clinical Practice (GCP) during the manufacture of the medicinal products and the clinical trials, respectively. The fact multiple manufacturing problems can affect each other is illustrated by the description of the problems surrounding medicinal product raw materials presented below.

Raw materials

As indicated above, medicinal product shortages may be caused by a problem with the raw materials. Raw materials can ‘run out’ due to a problem with (chemical) production of the raw material or because the source becomes exhausted. Active substances in a medicinal product must be produced in accordance with EU Good Manufacturing Practice (GMP) guidelines. Otherwise, they may not be used in medicinal products intended for the European Union (EU). The demands on manufacturers (and importers and wholesale suppliers) of active substances and medicinal products are defined in European legislation (Directive 2001/83/EC as amended) and related regulations.

Raw materials suppliers are currently not legally obligated to notify a competent authority if they expect a shortage of their product. Problems with raw materials suppliers are often acute; for example a government inspection with negative findings (GMP by the FDA, EU, etc.), unexpected problems with equipment, or natural disasters.

However, the involved medicinal product manufacturers are required to submit a notification. This may result in delays. However, raw materials are often ordered months in advance. If the manufacturer is informed that the raw material cannot be supplied, the manufacturer of the medicinal product may determine a medicinal product shortage is possible and report this.

The raw materials market is a global free market. A so-called API (active pharmaceutical ingredient) authorisation is required to import active substances into the European Union. In the Netherlands, Customs verifies whether the importing party has an API authorisation. Customs will stop shipments if no API authorisation is present, and contact IGZ as required. An API authorisation is also required for trading raw materials within the EU, and for the manufacture of active substances in the EU. The IGZ inspects companies with an API based on applicable GMP and GDP guidelines.

An API must also be included in the marketing authorisation dossier and may not simply be changed due to shortages experienced by the raw materials supplier, unless the new API is also included in the dossier. By including (if possible) multiple APIs in the registration dossier, a marketing authorisation holder may reduce the risk of shortages.
However, most raw materials are processed into medicinal products outside of the EU. For medicinal products, a declaration by a Qualified Person (QP) must be submitted with the application for marketing authorisation, stating that said person has audited the manufacturer of the active substance for GMP compliance. The QP must reside in the EU itself.

Additionally, there is also the so-called Certificate of Suitability to the monograph of the European Pharmacopeia (CEP). Companies that manufacture active substances can request such a certificate from the EDQM (European Directorate for the Quality of Medicines & Healthcare). The EDQM evaluates whether the quality of the active substance is sufficiently well-controlled based on the monograph of the European Pharmacopeia and, if necessary, using additional tests. The EDQM provides an inspection programme within the context of these CEPs. GMP is also evaluated during these inspections. Withdrawal of a CEP for a raw material following a negative inspection visit may impact the medicinal product market, particularly if it affects the only raw materials supplier for the medicinal product’s marketing authorisation holder.

Logistical problems

Logistical problems may be related to problems with planning or distribution. For example, the final product cannot be manufactured if a raw material shipment is delayed. Failure to comply with Good Distribution Practice (GDP) or manufacturers may impose quotas due to concerns about parallel exports. Additionally, shortages may develop due to a sudden increase in demand for a medicinal product, for example due to a shortage of another medicinal product with the same active substance.

Parallel trade

Export of medicinal products is an issue on the international stage. Due to price differences between countries, parallel trade can be a lucrative option for traders. After all, a medicinal product with a lower price in one country than another can be sold on with a profit. Shortages due to parallel trade are common in countries medicinal products are exported from.

Parallel trade brings cheap medicinal products to countries with high prices. If prices for medicinal products are low in the Netherlands, for example due to the Medicinal Product Reimbursement System (GVS) limit, the Medicinal Product Prices Act (WGP) limit or preferential policy, parallel trade from the Netherlands to other EU countries can be an interesting proposition. The major parallel import and export companies in our country are often linked to pharmaceutical wholesale suppliers.

Manufacturers / suppliers can monitor wholesale supplier orders to check whether the orders match demand in the Netherlands. This allows manufacturers / suppliers insight into any export, but also import of their medicinal products into the Netherlands. Manufacturers will want to prevent selling less in the country where prices are higher and more in the country where prices are lower (shifting their profit margin to parallel trade), but also that their product will sell out in the country from where it is being exported, or that they can no longer market their product in the country it is being exported to.

Commercial reasons

Shortages may also be due to a number of commercial considerations. The growing globalisation of the pharmaceutical market plays a role.

Mergers and acquisitions

Mergers and acquisitions result in a smaller number of suppliers, who subsequently rationalise their offerings or combine manufacturing facilities and reduce the number of raw materials suppliers they rely on. Product rationalisation may result in certain products disappearing or no longer being marketed in all countries. The diversity of medicinal product supply may reduce due to mergers. Mergers themselves result in fewer suppliers. Centralisation resulting from combining manufacturing facilities or trimming the number of raw materials suppliers reduces the possibilities
for addressing interruptions in the process. This makes the chain vulnerable. Problems with a single supplier with a large market share will naturally have a greater impact than problems with a smaller player.

*Leaving the market*

There are a number of reasons why a manufacturer may terminate delivery. The manufacturer may withdraw a product from the market because they consider the reimbursement is too low, the market is too small or due to parallel import that is considered undesirable. Another possible reason is that the medicinal product is not / no longer reimbursed because it is considered too expensive by competent authorities.

According to Bogin (and KNMP, BG Pharma), low prices (and thus low profit margins) in the Netherlands and unpredictability in the market are the main causes of shortages for multisource medicinal products. All parties in the column keep their stocks low to avoid the need to destroy products. Low profit margins make keeping stock relatively expensive due to storage costs. Less stock makes the chain more vulnerable to logistics problems, making delivery problems more likely. Health insurers indicate they have reduced uncertainties through a more timely indication of which products will be included in the preferential policy and longer appointment periods.
**PREVENTING SHORTAGES**

A number of the potential measures identified focus on preventing medicinal product shortages. These measures will be described per party below.

- **Government (Ministry of Health, Welfare and Sport, IGZ and MEB)**
- **Manufacturers**
- **Wholesale suppliers**
- **Pharmacists**
- **Health insurers**

It must be noted that the line between preventing shortages and addressing shortages cannot always be clearly drawn. Some measures for addressing shortages described in the following chapter also contribute to preventing them. However, preventing and addressing shortages are described separately, as the following chapter on addressing shortages describes all measures that are part of the roadmap.

**Government**

*Enforcement of the commitment to supply by manufacturers / wholesale suppliers and enforcement of timely notification of an expected shortage*

In the past, IGZ has focused primarily on contributing to solutions for actual shortages. Since early 2016, IGZ has explicitly taken the enforcement angle under consideration in its considerations regarding medicinal product shortages. Where shortages are concerned, IGZ is responsible for enforcing the commitment manufacturers have to supply wholesale suppliers and pharmacies (section 49 subsection 9 of the Medicines Act).

This also applies to timely notification of the Notification Centre, at least two months in advance, of an expected shortage (section 49 subsection 7 of the Medicines Act). Since the creation of the joint Notification Centre with IGZ, MEB has systematically monitored whether a company reports an expected shortage.

*Substantially increase penalty fee*

The penalty fee for violating the Medicines Act with regard to the commitment of marketing authorisation holders to supply wholesale suppliers and pharmacists and timely notification of expected shortages will be increased substantially. First, standard penalty fees were increased in the Ministry of Health, Welfare and Sport policy regulations on administrative penalties, from 45,000 Euro to 150,000 Euro. Second, draft legislation is currently under review to increase the general maximum penalty in the Medicines Act from 450,000 Euro to 820,000 Euro. This legislative proposal has been submitted to the House of Representatives. Standard penalty fees per violation can subsequently be increased based on this increase.

The standard penalty fee for a violation is the foundation for calculating the penalty fee. A range of penalty steps applies on top of the standard fee. Extenuating circumstances (for example the duration of a violation, culpability, etc.), aggravating circumstances (such as recidivism) and the size of the company are taken under consideration, with the size of the company being defined based on the number of employees.

The purpose of increasing the penalty fee is to ensure marketing authorisation holders are less likely to violate the Medicines Act in the domain of medicinal product shortages because they will be penalised proportionally in the event of such a violation. However, a number of parties also believe increasing penalties also means manufacturers of products with low turnover and/or price may decide to withdraw the product from the Dutch market because it will become a less attractive place to do business. Increasing the (maximum) penalty fee is not intended to scare off marketing authorisation holders to the point that they avoid the Dutch market. As indicated above, the penalty fee is stepped for reasons of proportionality. For multisource medicinal products, a second
marketing authorisation holder (label B) can generally not be held accountable for a shortage of his medicinal product due to increased demand resulting from a shortage of the first substance with the same active substance (label A).

*Greater surveillance of medication that many patients depend on*

Following a notification of a situation that may result in a shortage and a) cannot be resolved through pharmaceutical substitution and b) that the marketing authorisation holder considers there are insufficient alternatives, the Notification Centre shall perform an impact analysis to determine whether a medicinal product is considered critical. MEB / IGZ include the size of the potentially affected patient population in this analysis. For more information, see the roadmap in appendix 2.

Whether a medicinal product is considered critical in case of a shortage is determined based on, among other things, EMA criteria for GMP problems. These include factors such as the application of the medicinal product, for example whether it is intended for use in life-threatening conditions.

(If the medicinal product is considered critical, a decision may be made to keep the product on the market despite GMP concerns following careful consideration).

The word ‘critical’ in the term ‘critical medicinal product’ has a different meaning to the word ‘critical’ in a so-called ‘critical list’. A substance may be labelled as critical based on an impact analysis, after a notification. A critical list is drafted in advance.

The causes for medicinal product shortages are not addressed by drafting a critical list. Above all, there are practical implementation problems with drafting a critical list. The consideration of which substances belong to the category of critical medicinal products is a difficult and time-consuming process, the benefits of which do not justify the effort. Keep a stock of so-called critical medicinal products is also associated with costs. These costs will be included in the price of the medicinal product in question, and ultimately paid via health insurance premiums.

*Manufacturers / marketing authorisation holders*

*Measures to effectively prevent temporary unavailability*

The joint European innovative sector has drafted a best practice document and made it publicly available, so that all pharmaceutical companies, including those who are not members of the EFPIA (European Federation of Pharmaceutical Industries and Associations), can reduce the risk of shortages.

The approach to preventing and managing supply disruptions is built on three pillars:

1. managing disruptions in medical product supply is an integral part of the organisation,
2. where a holistic, end-to-end approach is laid down,
3. and risk management is implemented in order to identify the underlying root causes and address them, and to minimise the consequences.

As part of an extensive risk-management process, companies pro-actively take a broad range of potential causes on unavailability into account, including the risks of market dynamics, supply chain risks (both upstream and downstream) and manufacturing risks. Combined with a variety of risk-reducing strategies, this approach can often prevent temporary unavailability.

Continuous communication and information sharing with authorities and other parties about (potential) supply disruptions is also part of this approach. This encompasses the full spectrum from raw and base materials to intermediate products purchased from other suppliers, marketing authorisation holders themselves, wholesale suppliers, pharmacies, other care providers and the competent authorities.

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Despite this extensive, pro-active approach, potential or actual shortages may still develop. An approach designed to minimise consequences for patients in cooperation with other partners in the distribution chain and involved government parties is in place for such contingencies. Finally, proactive and reactive processes are linked to each other to allow course adjustments and maximum effectiveness.

Members of the Association for Innovative Medicinal Products in the Netherlands and the GLN shall be actively approached in the event of shortages to determine whether they may help prevent or limit said shortages. This is done in cooperation with MEB/IGZ.

**Fallback options for manufacturer in case of a calamity**

A default fallback option in case of a calamity such as a natural disaster is not the obvious choice, as every situation can/will be unique. Therefore, no consequences will be associated with this potential measure. What manufacturers may do is select multiple raw material suppliers (if possible) or multiple end-product suppliers in order to prevent shortages in the event of a calamity. This may be part of a manufacturer’s risk management strategy.

**Greater attention for commitment to supply (section 49 subsection 9 of the Medicines Act)**

Every manufacturer and every supplier of medicinal products has organised operational processes in such a way that the market demands can be met. In principle the demand is extremely clear: supply your medicinal products. In principle, it is in the best interest of the manufacturer / supplier to be able to supply these medicinal products. Only then can they generate the income required to operate a successful business. The inability to supply a medicinal product not only results in direct loss of revenue at that specific moment, but also in longer term loss of revenue. Patients who have switched to another medicinal product due to unavailability might possibly not be switched back to the original medicinal product once it becomes available again. The loss of revenue and thus income will thus persist for a longer period of time. Based on this perspective, manufacturers and suppliers will do their utmost to prevent a medicinal product from being unavailable.

Internationally, the European Plasma Protein Therapeutics Association (PPTA), the Association of the European Self-Medication Industry (AESGP), generic (Medicines for Europe) and innovative medicinal products (EFPIA) have jointly contributed to the effort on the part of the European Medicines Agency (EMA) to ensure patients in the European Union have continuous access to their medicinal products.²

**Take social responsibility for commercial decisions in order to prevent / limit consequences for the patient**

Of course, manufacturers may be expected to prevent problems for patients where possible. However, manufacturers have indicated they cannot be expected to keep a loss-making medicinal product on the market.

A timely notification - as soon as the company knows it shall terminate manufacture of medicinal products - is very important in order to allow other manufacturers to consider whether or not to take over this product or to allow an alternative to be investigated.

Manufacturers are already willing to adhere to a three-month term in case a manufacturer (particularly for products for which there is only one manufacturer in the market) wishes to withdraw supply of a medicinal products, to allow MEB to evaluate the consequences and discuss the matter with the marketing authorisation holder. During this investigation, the manufacturer shall maintain the marketing authorisation for a maximum period of three months. The manufacturer shall keep the product on the market during this period.

The MEB and IGZ procedure provides for the party with supply problems to seek out an alternative itself; MEB only ascertains that a medicinal product is leaving the market and subsequently publishes this information. Within this context, the results achieved in the dialogue between MEB and other manufacturers interested in taking over such medicinal products if manufacturers wish to withdraw them from the market should be considered.

The MEB has a withdrawal application form available on its website. If withdrawing the medicinal product results in problems for the patient, the MEB shall investigate alternatives for keeping the product on the Dutch market. This is usually done in consultation with the manufacturer. MEB publishes a list of intended withdrawals, so other manufacturers can take note and be given the opportunity to take over the medicinal product. The planned withdrawal becomes final six months after publication of the overview.

Both marketing authorisation holders and MEB handle such matters with the utmost care. An overview of which marketing authorisations for medicinal products were withdrawn in 2016 is available on the MEB website. This lists 31 withdrawals after considering patient interests. For 30 of the 31 withdrawals, MEB concluded there were sufficient alternatives. For the 31st withdrawal, the medicinal product can be imported, as the company has committed to continuing to guarantee supply of the product based on a European marketing authorisation.

It should be noted that manufacturers believe that while withdrawing marketing authorisation or removing the product from the assortment does lead to permanent unavailability of a product, this does not necessarily result in a shortage. According to manufacturers, there can be no (more) shortage if a medicinal product is not available in the market. However, from a patient perspective, a shortage may certainly exist. The definition of a shortage from a patient perspective, in brief, is: "An interruption of the supply of a medicinal product that cannot be addressed via pharmaceutical substitution." Permanent (and temporary) unavailability may, depending on the medicinal product, also result in significant problems for the patient according to both pharmacists and patients. Therefore, the above-mentioned diligent MEB procedure is of vital importance.

**Wholesale suppliers**

**Set up early warning system**

In order to gain better insights in decreasing suppliers, wholesale suppliers have been asked to develop an early warning system for decreasing wholesale supplies due to failure to receive medicinal products from a manufacturer as a result of e.g. manufacturing issues, quotas or other economic motives.

BG Pharma has addressed this request and agreed that associated wholesale suppliers shall notify BG Pharma (trusted party) of decreased supplies due to inability to obtain a specific medicinal product. The procedure agreed upon by the wholesale supplier to signal decreasing supplies is based on uniform, objective and testable definitions:

- In the event of a severe shortage, BG Pharma is notified if supply levels drop below three days (by the wholesale supplier).
- Once BG Pharma has received a notification, it shall request information about this specific medicinal product from other wholesale suppliers within 24 hours. BG Pharma shall assess the inventory and determine how long the supply problem is expected to persist.
- Under exceptional circumstances, BG Pharma may notify the Medicines Shortages and Defects Notification Centre about a supply problem and how long this is expected to persist. Before such a notification is submitted, the manufacturer in question is contacted and asked to report the supply problems if this has not yet been done.

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This early warning system thus serves as a back-up system for identifying potential supply problems.

**Make agreements to prevent shortages due to export**

To prevent shortages from developing in the Netherlands due to parallel trade, wholesale suppliers have made an agreement stating that in the event of a potential or actual shortage, they shall forego exports that may result in (further) shortages in the Netherlands. This means that the wholesale supplier shall take its primary customers into account before considering export of medicinal products.

These agreements are documented in a code of conduct:

- Every wholesale supplier imports and exports medicinal products. This so-called parallel trade is a (small) part of business operations.
- The wholesale supplier shall always serve its own clients in the Netherlands first (pharmacies, hospitals, dispensing GPs, etc.). In the event of a potential or actual shortage of a specific medicinal product, export shall only take place once own supplies have been checked and deemed sufficient.

**Pharmacists**

**Supply security in contracts with wholesale suppliers**

Demanding supply security via contracts is not a solution for causes wholesale suppliers cannot affect. Such contracts would require too many exception clauses. Such disclaimers would result in contracts that fail to address the targeted issue. Furthermore, the wholesale supplier shall always endeavour to do its utmost to supply its clients. Therefore, no consequences will be associated with this potential measure.

**Health insurers**

**Supply security in contracts with manufacturers**

Including agreements about supply security in contracts and entering into contracts for longer periods should result in fewer or less severe shortages. Health insurers do not enter into contracts with wholesale suppliers, only with manufacturers. Insofar as health insurers make agreements with manufacturers regarding purchasing policy, a form of supply security is included in their contracts. This is the case if preferred medicinal product policy is implemented.

Purchasing policies differ among health insurers, but there are commonalities. With regard to supply security, health insurers have included the following items, in some form, in their contracts:

- If a contract has been entered, delivery is mandatory;
- Periodic (weekly or bi-weekly) reports of supply status for the health insurer;
- Penalty clause in the event of unavailability;
- Suppliers must have a contingency plan;
- Selection of another supplier for as long as supply problems persist.

This list is not exhaustive, and not every health insurer has included these items in equal detail in their purchasing policy. However, it may be stated that when health insurers enter contracts with manufacturers, they include clauses on unavailability. These contracts were recently updated in order to prevent medicinal product shortages. In the event of a shortage of a preferred medicinal product, health insurers shall identify an alternative medicinal product for their preferred product policy.
A separate version is the lowest price guarantee. As no contract is entered into with a manufacturer in this case, supply security is sought through a lowest price guarantee with a defined bandwidth.

Health insurers have previously taken the initiative to assign the lowest-priced preferred medicinal products a distribution bonus in order to ensure distribution remains possible. This measure has had a positive impact.

_Earlier notification of preferred medicinal products_

All health insurers with some form of preferred medicinal product policy have a long prelude before the policy comes into effect. This varies between three to six months. The current periods should be sufficient, according to the manufacturers.

Health insurers will indicate which products they no longer intend to identify as preferred in the coming year. This will allow the market more time to prepare.

_Broader implementation of the preferred medicinal product policy_

It is clear that preferred medicinal product policy results in significant price drops during the first one and a half to two years after a medicinal product loses its patent protection and generics become available. There is no consensus within the working group regarding expanding preferred medicinal product policy to prevent supply problems by identifying multiple products as preferred. A clear and direct relationship between preferred medicinal product policy and supply problems cannot be established. Health insurers understand problems experienced by patients and pharmacists if a preferred medicinal product is unavailable and patients are forced to switch medication. Switching as such does not result in medicinal product shortages, as another substance with the same active substance is often available. Pharmacists and health insurers will jointly investigate how to reduce the impact for patients.
ADDRESSING SHORTAGES

The working party has created a roadmap to follow in the event a notification submitted to the Notification Centre results in a situation that may lead to a shortage (see Appendix 2). The procedure to be followed is thus clear in advance. The roadmap also describes who is involved at what stage. The routes on the roadmap must also be administratively and economically viable. Therefore, the reimbursement per route is described (Appendix 3). Pre-existing bottlenecks have been discussed by the working party in recent months and resolved where possible.

Communication is another aspect of the roadmap. In the event of a medicinal product shortage from a patient perspective, MEB/IGZ are ultimately responsible for communication, but they may issue a mandate for other parties to take responsibility or the lead in communications, depending on the situation. The key issue is ensuring coordinated communications. Good and timely information for patients, practitioners, pharmacists and other involved parties can prevent misunderstandings and unrest.

The roadmap will be applied to any shortages that develop in the upcoming months. This may result in changes to the roadmap over time based on experience.

The routes and other measures are described below per actor (government, manufacturer, wholesale supplier, pharmacists, health insurer).

**Government**

*Temporary deviating packaging*

IGZ can authorise the marketing authorisation holder to temporarily supply the medicinal product in a deviating packaging (TDV). Deviating means: other than described in the marketing authorisation dossier. Other than the packaging, the replacement product is entirely identical and manufactured in the same place as the product authorised in the Netherlands. This applies to a small batch, for a limited time (generally no more than three months). Packaging is supplied with a Dutch package leaflet or a copy of the authorised Dutch package leaflet text is included.

Requests made for solely commercial reasons, such as low turnover of the product in the Netherlands, shall be denied. The MEB is developing policy for drawing the attention of manufacturers to multi-language packaging (that a manufacturer may market in multiple countries) or English-language packaging. This may be a solution for commercial unavailability of products for small patient groups (e.g. child formulations) in the Dutch market, which would otherwise not be lucrative enough for the manufacturer due to the small market.

*Exception repackaging imported packaging for intramural use is not necessary*

In order to obtain permission to supply a medicinal product in a temporary deviating packaging, conditions including those described above are often applied. An exception may be made for medicinal products used solely intramurally. This is because the patient generally does not see the packaging within the hospital.

*Possibility for stocking unauthorised medicinal product*

Current IGZ policy is that for unauthorised medicinal products with permits granted in accordance with section 40, 3rd subsection, under c. of the Medicines Act to supply the product based on a physician's declaration, and that must be usable ad hoc (e.g. in an ICU or OR), a small stock may be maintained by the pharmacy, wholesale supplier or manufacturer. Furthermore, supplies intended for an existing patient or patients who will soon require treatment may be created.
Pharmacy preparations

In the event of shortages, officinal or compounding pharmaceutical products may be a solution for own patients. This possibility is an exception (via section 40 subsection 3 under a) to the general section of the Medicines Act that prohibits marketing of a medicinal product without marketing authorisation issued by the EC or MEB (e.g. section 40 subsection 1 of the Medicines Act). This exception does not apply to peer forwarded pharmaceuticals, as this does not concern provision of medicinal products to an own patient. Forwarded pharmaceuticals do meet a need, however. In August 2016, IGZ allowed forwarding of own pharmaceuticals under certain conditions. The principle is that forwarded pharmaceuticals must (also) be possible in the (commercial) absence of authorised adequate alternatives, i.e. if a medicinal product is not available on the Dutch market.

Marketing authorisation for reasons of public health ("Section 52")

In the event of a medicinal product shortage, MEB may grant marketing authorisation for reasons of public health. MEB takes the initiative in this case. This means that a company becomes a marketing authorisation holder for a medicinal product authorised in another EU member state and markets it in the Netherlands ‘at the request of the MEB’.7

No application is submitted; marketing authorisation is issued to a legal person who, in the opinion of the MEB, qualifies. The manufacturer does not need to pay for this marketing authorisation, as the MEB issues said authorisation without an application. Payment is usually for the application procedure. It is important that the party receiving the marketing authorisation be able to agree to said authorisation and all of the responsibilities it entails.

A marketing authorisation for public health reasons can only be issued if the health of a large group of patients would be impacted negatively due to a medicinal product no longer being available and the lack of an alternative. Marketing authorisations for public health reasons are temporary. For example, as soon as a medicinal product authorised via the regular route is marketed, the marketing authorisation shall expire.

Because marketing authorisations for public health reasons are an exception to the regular procedure for marketing authorisation, the exceptions must be interpreted strictly. To date, no such marketing authorisation has been issued by the MEB. The possibility to actually issue such a marketing authorisation was created in late 2016 to ensure the option exists should the situation call for it.

Accelerated mutual recognition procedure

The mutual recognition procedure is a European marketing authorisation procedure based on the principle of recognition of the evaluation performed by the reference member state. If another European member state has already issued a marketing authorisation, the Netherlands can mutually recognize the marketing authorisation based on the evaluation report by said member state. The procedure required for this process is accelerated by the MEB in the event of a medicinal product shortage.

Parallel import marketing authorisation

If a medicinal product is imported from other European countries, this is called parallel import. In case of parallel import, the medicinal product is marketed in the Netherlands by an importer not appointed by the original marketing authorisation holder. In such cases, an identical or quasi-identical medicinal product is already authorised in the Netherlands; the so-called Dutch reference medicinal product. The price of a medicinal product may be lower in the other member state. Therefore, it may be economically attractive to market a medicinal product via parallel import. This requires a parallel import marketing authorisation from the MEB.

7 This option is described in section 52 of the Medicines Act. This is the national legislative implementation of section 126bis of Directive 2001/83/EC.
The marketing authorisation procedure for parallel import products does not apply to medicinal products with marketing authorisation issued by the European Commission which applies in the entire European Commission, a so-called community marketing authorisation. In such cases, a notification must be submitted to the EMA.

**Changes to existing marketing authorisation dossier**

In the event of a potential medicinal product shortage due to manufacturing problems, the marketing authorisation holder may submit a change to the product, for example a change in its composition or different packaging, or addition of another manufacturing site or raw material site to the medicinal product dossier. In case of a shortage, the MEB shall process applications of this nature more quickly. In some cases, marketing authorisation holders already have multiple raw material suppliers and/or manufacturing sites listed in the dossier, and may thus avoid situations that could result in shortages.

**Reimbursement of imported medicinal products not authorised in the Netherlands (“1:150,000”) and of medicinal products with a marketing authorisation for public health reasons (within the meaning of Section 52 of the Medicines Act)**

One obstacle in the regulations that applies to reimbursement for imported medicinal products will be removed in the future. Currently, imported extramural medicinal products that are not authorised in the Netherlands (with the exception of medicinal products for orphan diseases, the so-called 1:150,000 regulation) do not qualify for reimbursement under basic insurance coverage. Health insurers sometimes reimburse such products for humanitarian reasons. If this is not the case, the pharmacy or the insured party bears the costs. This is an undesirable situation, as the medicinal product of which there is a shortage would be reimbursed via the Medicinal Product Reimbursement System (GVS). (This issue does not apply to medicinal products for intramural use). The intention is to allow reimbursement of extramural medicinal products not authorised in the Netherlands via health insurance in the event of a medicinal product shortage.

**Simplified procedure for physician declaration**

The underlying principle in the Medicines Act is that a medicinal product may only be marketed if authorised. There are a number of exceptions to this. One such exception is important for addressing medicinal product shortages. It concerns medicinal products that are dispensed based on an order at the initiative of a physician for his individual patients, and that are imported or otherwise brought into the Netherlands at said physician's request. This import occurs via another European Union member state or a third nation where said medicinal products are marketed. Prior permission from IGZ is required for this exception. This exception is included in the Medicines Act. The medicinal product may be delivered to a physician if the physician deems it necessary that his patient be treated with the medicinal product, there is no adequate pharmacological alternative to the medicinal product marketed or otherwise available in the Netherlands, the physician has requested dispensation of the medicinal product in writing, the request has been submitted to IGZ, and IGZ has determined what amount of the medicinal product and during what period said product may be dispensed to the physician in question.

For an initial application, IGZ requires a fully completed physician declaration. In general, in the event of shortages - particularly shortages of alternative medicinal products that are authorised in another member state - permission will be granted per indication. This means prior permission does not need to be requested from IGZ for each individual patient.

Subsequently, the party who has been given permission is obligated to keep (a copy of) the physician declaration in his own personal records for each patient treated with said medicinal product. Thus, the physician declaration need not necessarily be submitted to IGZ per patient in order to receive permission. In the event of an inspection, IGZ may review the physician's records for compliance with the law. If the need for the medicinal product remains after one year -
permission is generally granted for one year - the applicant must submit a request for an extension and indicate the number of patients treated with the medicinal product in question.

The power granted to MEB based on section 52 of the Medicines Act to issue marketing authorisation without an application is expected to reduce the number of physician declarations required. This addresses complaints by physicians and pharmacists regarding the administrative burden of the physician declaration process. Not all medicinal products currently dispensed via a physician declaration shall be issued a marketing authorisation by the MEB in accordance with section 52. Although section 52 of the Medicines Act is one of the options on the roadmap, the physician declaration shall also remain a possible route. The physician declaration shall remain necessary for importing medicinal products not authorised in the Netherlands from outside of the EU, and also in cases where no shortage exists, for example for clinical research.

**Manufacturers**

*Bill costs of unavailability to parties that affect this*

The price of a large number of medicinal products is low thanks to preferred medicinal product policy. The success of this preferred medicinal product policy has translated into substantially lower spending on pharmaceutical care in recent years, and thus in lower insurance premiums. Holding manufacturers and suppliers liable for penalties and costs is a fallacious solution, according to manufacturers. Manufacturers will include the potential risk of a penalty fee and may choose to offer less competitive prices in order to build a buffer.

If the preferred medicinal product cannot be dispensed, the pharmacist may select one or more non-preferred authorised medicinal products indicated by the health insurer. If a preferred medicinal product is no longer available, another (potentially) more expensive (and sometimes cheaper) medicinal product will (temporarily) be dispensed by the pharmacy. These costs are covered entirely by the health insurer, unless the health insurer and pharmacy have agreed otherwise. The patient does not need to pay an additional sum if the price of the more expensive medicinal product is below the GVS limit.

The additional costs for patients (or pharmacists) associated with dispensation of a more expensive medicinal product in the event of a shortage are addressed explicitly in (contract) negotiations between generic manufacturers and health insurers.

Manufacturers also point to the possibility of parallel export or distribution by wholesale suppliers resulting in shortages. This creates conditions of which manufacturers cannot be expected to bear the consequences.

**Wholesale supplier**

*Rapid insight into supplies*

Wholesale suppliers shall provide rapid insight into their supplies via BG Pharma (trusted party) at the request of MEG/IGZ, to ensure the supplies of a specific medicinal product can be determined quickly in the event of a shortage. This measure is already operational at the European level, with supplies for various wholesale suppliers in Europe being combined virtually should the situation require it.

The following procedure is followed:

- BG Pharma requests supply levels for the specific medicinal product from all wholesale suppliers within 24 hours of receiving a request, and asks how long the supply problem is expected to persist.
- BG Pharma determines total supply of the specific medicinal product at wholesale suppliers.
- BG Pharma informs MEB/IGZ of the total supply of the specific medicinal product and how long the total supply can meet market needs.
Wholesale suppliers could potentially redistribute supplies amongst themselves. However, this is difficult to organise. Furthermore, in dire need, supplies will likely be too low to redistribute. In order to address truly urgent cases, an ad-hoc approach via the sector organisation is preferred.

Set quotas for delivery to pharmacies in case of shortages

One of the routes on the roadmap is setting quotas for deliveries to pharmacies. This means that in case of (potential) shortages, quotas will be set for deliveries to pharmacies based on historical deliveries in order to prevent stockpiling by pharmacies and/or patients, and ensure fair distribution among pharmacies and patients. The decision to take this route will be taken by the Notification Centre’s Operational Team.

Wholesale suppliers within BG Pharma have documented this agreement in a code of conduct: In the event of (potential) shortages of one or more specific medicinal products, wholesales shall, at the request of the Operational Team of the MEB/IGZ, set quotas for pharmacies based on historical delivery information if there are signs that pharmacies are ordering more than normal based on historical information, so-called stockpiling. This promotes equitable distribution among pharmacies.

Pharmacists

Dispensation agreements for pharmacists in case of shortages

A situation may develop in which supplies are present, but insufficient to serve all patients. Dispensation agreements can contribute to reducing the problem. In consultation with prescribers, pharmacists and patient representatives, the MEB/IGZ Operational Team may ask pharmacists to only dispense the medicinal product to the most vulnerable patients or only in more limited amounts until such time as supplies are adequate. There must be prospects for return of the medicinal product for which there is a shortage. This is one of the routes on the roadmap that may be selected, including the related communication strategy. Pharmacists have indicated they are willing to cooperate with such efforts.

Health insurers

Recover damages from manufacturer?

Sometimes patients suffer financial damages due to a shortage. For example because additional costs are billed to the deductible. Health insurers could spare insurees whose deductible is affected because they need to switch to a more expensive medicinal product, but they do not, partly because a significant proportion of patients already pay the full deductible. The government does not reimburse such costs because patients often face costs they cannot do anything about. Reimbursing such costs would also set an undesirable precedent.

Health insurers could sue on behalf of their insurees. However, if health insurers do not have a contractual relationship with the manufacturer, suing on behalf of the patient is more risky and expensive.

Health insurers could hold the manufacturer responsible for their own damages. If a manufacturer is held in default by IGZ, the manufacturer may be held liable for a wrongful act. This path can also be followed by other parties. The suffered damages can be recovered through civil proceedings.

Increase of litigation in health care as such is undesirable, but the knowledge that a suit could be filed may prevent careless actions on behalf of a manufacturer.

Bill costs of unavailability to parties that affect this

In the past, the financial consequences for the pharmacy and patient were unclear if an alternative was prescribed in the event of a shortage. The roadmap identifies the different situations and
indicates reimbursement per route. The principle is that financial consequences for the patient must be minimised, although costs for items other than medication may exist, such as diagnostic testing or additional consultations. Communication with the patient is very important in all such cases.

**International**

*Active participation in EMA shortages task force*

The MEB participates actively in the HMA/EMA Task Force on availability of authorised Medicines for human and veterinary use on behalf of the Ministry of Health, Welfare and Sport. The scope is wider than shortages due to GMP problems.

Furthermore, the MEB is active in European discussions about shortages via the Co-ordination group for Mutual recognition and Decentralised procedures (CMDh) and the Committee for Medicinal Products for Human Use (CHMP).

During the EU Presidency of the Netherlands during the first half of 2016, attention was also given to medicinal product shortages. The Council Conclusions ratified during the Dutch presidency of the EU called on the European Commission to explicitly give attention to notifications on the European medicinal product market. Commissioner Verstager has since indicated she will follow-up on these council conclusions during a number of sessions of the European Parliament.

The issue of medicinal product shortages was also a prominent item on the agenda during the Slovakian EU presidency in the latter half of 2016. The Netherlands called on other member states to exchange information between member states about national shortages and about national requirements defined for the pharmaceutical industry in order to prevent shortages.

Additionally, a number of different European competition cases were heard before the European Court of Justice, which among other things addressed ‘pay for delay’, in which severe fines were levied on pharmaceutical manufacturers. National regulators are also actively involved in the matter.

Other topics on the European agenda include whether further commentary or elaboration of the legal responsibilities of marketing authorisation holders is desirable. Additionally, the questions of how to keep unprofitable but important medicinal products available and whether manufacturers can be obligated to market certain medicinal products in all member states when applying for EU marketing authorisation were on the table.

Medicinal product shortages are also a subject of discussion in other countries. For example, the German government initiated a Pharma dialogue about supply problems (‘Jour Fixe’ zu Liefer- und Versorgungsgpässen) with the sector in September 2016. Manufacturers have committed to endeavour to prevent shortages.

A report was recently published calling for all actors in the medicinal product chain - manufacturers, parallel importers, wholesale suppliers and pharmacists - to improve collection and publication of information in the event of medicinal product shortages. The purpose of these efforts is to reduce the impact of medicinal product shortages. The stakeholders make recommendations for creating an ideal information system and present best practices.

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8 [http://www.bfarm.de/DE/Arzneimittel/zul/amInformationen/Lieferengpaesse/jourfixe/_node.html](http://www.bfarm.de/DE/Arzneimittel/zul/amInformationen/Lieferengpaesse/jourfixe/_node.html)

9 “Als weiteres Ergebnis des Pharmadialogs hatte sich die pharmazeutische Industrie verpflichtet, durch weitere Optimierung ihrer Prozesse und des Qualitätsmanagements zu einer Verbesserung der Versorgungssituation beizutragen.”

Closing comments

There are a number of developments that may affect medicinal product shortages in the future, such as European Directive 2011/62/EU 'Falsified Medicines Directive', passed in order to prevent falsified medicinal products from entering the legal medicinal product distribution chain or further consolidation of the medicinal product market. Therefore, it is important to continue tracking such developments.

The working group will therefore meet periodically in the future in order to discuss the topic of medicinal product shortages. The analyses performed by the Notification Centre will be included in this process. Additionally, all agreements made will be monitored.
Appendix 1: Working party members

Government:
- Medicines Evaluation Board (MEB): Mrs. S. Kruger
- Health Care Inspectorate (IGZ): Mr. R. Jansen, Mr. M. van Berlo
- Ministry of Health, Welfare and Sport: Mr. W. de Haart (chair), Mr. E.J. van Asselt (secretary), Mrs. S. Scherpenisse (secretary), Mrs. M. Velema (office)

Manufacturers:
- Association for Innovative Medicines in the Netherlands (VIG): Mr. A. Voorschuur
- Dutch generic and Biosimilar medicines association (BOGIN): Mr. M. Favié
- Generic Suppliers the Netherlands (GLN): Mr. J. Broeren, Mr. J. Bruin

Wholesale suppliers:
- Association of Wholesale Suppliers in the Pharmaceutical Industry (BG Pharma): Mr. G. Aldershof
- Mosadex: Mr. L. Castelijns

Health insurers:
- Health Insurers Netherlands (ZN): Mr. M. Potjens
- VGZ: Mr. S. Zarroy
- Zilveren Kruis: Mr. F. Visser
- Menzis: Mr. H. Eleveld
- CZ: Mr. R. van Oosterhout

Pharmacists
- Royal Dutch Pharmacists Association (KNMP): Mr. L. Tinke, Mrs. D. Postma
- Association Chain Pharmacies (ASKA): Mr. S. Veenstra
- Dutch Association of Hospital Pharmacists (NVZA): Mr. C. van Loosen, Mr. B. van den Bemt

Medical Specialists:
- Federation of Medical Specialists (FMS): Mrs. B. van de Lagemaat

Patients:
- Patient federation: Mr. J. Benedictus
Appendix 2

Roadmap for handling of notifications of medicinal product shortages

Version 9 March 2017

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1. Introduction

At the Medicine Shortages and Defects Notification Centre\textsuperscript{11} of the Medicines Evaluation Board (MEB) and the Health Care Inspectorate (IGZ) (hereafter: the Notification Centre) inform marketing authorisation holders of the following:

a) A medicinal product is placed on the market for the first time or again following on an interruption. This requirement does not apply to parallel import marketing authorisations.

b) Marketing of a medicinal products is being discontinued or interrupted (including a possible shortage). This requirement does not apply to parallel import marketing authorisations.

The following definition applies: \textit{“If a marketing authorisation holder temporarily suspends marketing a medicinal product, while there is still sufficient stock of the own product on the market, at wholesale supplier and pharmacies, such that the interruption does not result in shortages, no notification is required.”}

This definition automatically entails that notification of permanent termination of marketing a medicinal product is always mandatory.

This is a notification within the meaning of section 49.7 of the Medicines Act.

c) A quality defect exists in a medicinal product.

If a quality defect results in a shortage, the marketing authorisation holder shall also report this. The form automatically leads the notifying party to the questions that are also asked after a notification under (b).

d) A potential shortage may develop because a medicinal product is available in smaller quantities or to an insufficient degree. This is not a notification within the meaning of section 49.7 of the Medicines Act, but is relevant information for preventing medicinal product shortages. Furthermore, based on section 49, subsection 9 of the Medicines Act, a company has a duty of care to maintain stocks of a medicinal product adequate for serving the needs of patients.

The Working Party of Medicinal Product Shortages concluded that marketing authorisation holders are obligated to submit a notification of shortages. The Notification Centre was established within the context of this Medicines Act requirement. Pharmacies and wholesale supplier may report warning signs to the marketing authorisation holder. In the event of an actual shortage, the

\textsuperscript{11}www.meldpuntgeneesmiddeltekortendefecten.nl
marketing authorisation holder shall subsequently notify the Notification Centre. Thus, the Notification Centre is not a place where pharmacists and wholesale supplier can report shortages.

2. Types of notifications and follow-up actions

This roadmap only describes what happens with a notification of marketing of a medicinal product being stopped or interrupted, or if a medicinal product is temporarily available in smaller quantities or is insufficiently marketed; these are the notifications described above under (b) and (d). The roadmap does not describe what happens with a type (a) or (c) notification where no shortage is expected.

Upon receiving a type (b) or (d) notification, MEB/IGZ evaluate whether a shortage will develop. MEB/IGZ apply the following criteria when evaluating whether a shortage will occur, which are also applied to withdrawal of marketing authorisations:

- Are there are enough other authorised and available medicinal products with the same active substance, strength and pharmaceutical form that are authorised for the same indication? Market share is considered in this evaluation: the smaller the market share, the greater the odds other companies will be able to compensate for the shortage.

The marketing authorisation holder can also estimate whether there are sufficient alternatives when submitting the notification.

- If the answer is ‘yes’, this is not defined as a shortage, but as a notification. The situation is similar to that of substitution of generic medicinal products. The notification is documented, but the Notification Centre does not take any further action or communicate about the matter. It is the responsibility of the marketing authorisation holder to communicate this information to its clients, pharmacists and any health insurers with whom agreements have been made. Items to be addressed in communications as listed in chapter 4.1.1 must also be considered.

If the Notification Centre receives such notifications for comparable medicinal products from multiple marketing authorisation holders at the same time, MEB/IGZ will take action. The Notification Centre is responsible for providing an early warning in such cases. Should the Notification Centre receive such notifications from a company erroneously (e.g. the company states sufficient alternatives exist, but this is found not to be the case), MEB/IGZ shall consult with the company.
• If the answer is ‘no’ or ‘unknown’, this is considered a possible shortage. It must be determined whether it involves a critical medicinal product. The criteria defined by the European Medicines Agency\textsuperscript{12} for evaluating whether a medicinal product is critical in case of GMP problems or quality defects are used. Among other things, an evaluation of whether the medicine is part of the treatment for a disease that is life-threatening or irreversibly progressive, or whether the patient will suffer harm if treatment is stopped will be performed. However, MEB/IGZ also evaluate whether the medicinal product is difficult to replace, consulting with practising physicians and pharmacists in their network in order to make this determination. This evaluation is similar to the procedure applied by MEB when withdrawing a marketing authorisation that MEB believes may harm patient interests. In late 2016, MEB only performed this evaluation if a company submitted a request for withdrawal of marketing authorisation, but since the introduction of the Notification Centre, MEB shall perform this evaluation as soon as the company reports it will stop marketing the medicinal product.

3. Possible alternatives

Once it has been concluded that there is a shortage and that the medicinal product in question is critical, alternatives will be sought.

Depending on the scope and duration of the shortage, the steps below are completed in the order shown or in another order. The first step is always to check whether an alternative product is authorised in the Netherlands. Other potential solutions are sometimes investigated in parallel. Different solutions may also follow one another over time: this means a temporary solution has been found.

European coordination is required for a number of actions, but this is not listed separately per action.

The possible alternatives and actions taken by the Notification Centre are presented below.

1. If an alternative product is authorised in the Netherlands that contains the same active substance:
   o Insight into market share: information is collected by MEB from the Foundation for Dutch Pharmaceutical Key Figures (SFK) for extramural medicinal products. No good database is available for intramural medicinal products that provides rapid insight

into market share; the marketing authorisation holder is asked to provide this information.

- Can the other company scale up manufacturing? Consultation with the other marketing authorisation holder will be required for this. If the other marketing authorisation holder makes demands for scaling up manufacturing, the Ministry of Health, Welfare and Sport is contacted.

- If the medicinal product is authorised via a centralised procedure, a mutual recognition procedure or a decentralised procedure (so an identical product exists in another member state), the marketing authorisation holder must investigate the possibility for redistribution of supplies at the European level. If this is possible, a Temporary Deviating Packaging is a solution.

- If the product is authorised via a national procedure and the company can show that an international product is identical, then review the possibilities for redistribution of supplies at the European level together with the marketing authorisation holder. If this is possible, a Temporary Deviating Packaging is a solution.

If no solution can be found based on the possibilities listed under (1), alternatives will be sought. The marketing authorisation holder will also be asked to investigate these possibilities, and depending on the input received by MEB/IGZ from the marketing authorisation holder, MEB/IGZ will determine whether a question will be shared widely within the Operational Team among members that represent marketing authorisation holders and wholesale supplier. This allows multiple companies to look for solutions and submit proposals. The matter of confidentiality is currently an area for attention. In cases of a possible medicinal product shortages, the question remains whether sharing this information widely will lead to too much unease and stockpiling. This is a consideration MEB/IGZ will make in each individual case.
2. If an alternative product is authorised in the EU
   - If a comparable (but not identical) medicinal product is authorised internationally:
     investigate the possibility of parallel import marketing authorisation, mutual
     recognition procedure and marketing authorisation procedure for reasons of public
     health (based on section 52 of the Medicines Act). Include the possibility of a
     Temporary Deviating Packaging as soon as the product is authorised.
   - Investigate the possibility for an individual physician declaration (section 3.17
     Medicine Law Regulation).

   The marketing authorisation holder for the medicinal product of which there is a shortage
   may play a role.

3. If an alternative product is authorised outside the EU, or there is an unauthorised medicinal
   product in the EU:
   - Investigate the possibility for an individual physician declaration (section 3.17
     Medicine Law Regulation).
   - Investigate the possibility of forwarded preparations.

4. Investigate the possibility for making changes to the existing marketing authorisation, e.g.
   accelerated approval of a new manufacturing site or other packaging.

5. In an emergency, intervention into the supply to or treatment of patients may be considered
   (e.g. only treat specific patient groups, lower the dosage, postpone treatment for certain
   patient groups, non-pharmacological treatment, supply the patient for a shorter amount of
   time). For all such solutions, MEB/IGZ will ensure clear communication for prescribers,
   patient associations, pharmacies and/or wholesale suppliers. Depending on the possible
   solutions, these parties and the marketing authorisation holder will also be involved in
   deciding which solution is best.

6. Redistribution of supplies between pharmacies and wholesale supplier. This is not legally
   permitted and thus may only be considered in case of a dire emergency. If this solution is
   selected, MEB/IGZ will take responsibility for clear communication with pharmacies and
   wholesale supplier.
4. The solution and follow-up

If no solution has been found, but it is already clear the impact will be significant, health insurers, wholesale supplier, pharmacies, prescribers and patient associations will also be informed. This must occur under an embargo in order to prevent unease and stockpiling.

For follow-up, a distinction needs to be made between various types of solutions:

a. The alternative medicinal product is authorised in the Netherlands with the same active substance and comparable strength and pharmaceutical form. This situation is comparable to generic substitution.

b. The alternative medicinal product is authorised in the Netherlands with the same active substance, but it does not have a comparable strength and/or pharmaceutical form, or the alternative medicinal product is authorised in the Netherlands with the same active substance and a comparable strength and pharmaceutical form, but it is a medicinal product that requires additional attention where substitution is concerned.

c. The alternative medicinal product is authorised in the Netherlands with a different active substance.

d. The alternative medicinal product is not authorised in the Netherlands. This is then based on an individual physician declaration (section 3.17 Medicine Law Regulation) or a (forwarded) pharmacy preparation.

   Such substances should preferably be submitted for the G standard by the supplier. This ensures medication vigilance and declarations/reimbursement are ensured.

e. An intervention is made in the treatment (specific target group, lower dose, postponing treatment, non-pharmacological treatment, shorter period of supply to a patient).

To clarify: The solution ‘The alternative medicinal product is authorised in the Netherlands’ means a normal marketing authorisation, parallel import marketing authorisation or a marketing authorisation without an application (section 52). However, it may be supplied in foreign packaging (via the section 52 procedure if the MEB waives the requirement for Dutch language packaging, or if IGZ authorises a Temporary Deviating Packaging). In both situations, the principle is that there is a label on the box listing (among other things) the RVG number, the Dutch product name and the name of the authorisation holder, and a Dutch language package leaflet is included. This procedure is similar to a parallel import marketing authorisation.
In emergency situations, however, this requirement may be waived (e.g. medicinal products that are used intramurally).

4.1 Communication

General points for attention regarding communication:

- Address the cause of the (potential) shortage in communications.
- Address the choice of alternative in communications: explain why an option has been selected.
- In communications addressing patients, distinguish between medicinal products for chronic or single use. The impact of a replacement medicinal product for a patient is absent/less significant if the medicinal product is for single use (the patient does not need to switch medication).
- Communications and the timeline may be well-prepared, but as soon as information becomes public and enters the press, communication must be accelerated.
- The information requirements of the LHV (Dutch Association of General Practitioners) Dispensing Department (LHV AHA) are comparable to those of the Royal Dutch Pharmacists Association (KNMP). The LHV AHA and the KNMP could jointly consult Health Insurers Netherlands about reimbursement status. If LHV AHA is not present during this consultation, it must be informed directly by KNMP/ZN about the outcome of the discussion about the reimbursement status of the alternative.
- MEB/IGZ coordinate communication and tailor it in consultation with parties in the Operational Team (OT) and the marketing authorisation holder, as appropriate. It is important for all parties to communicate a common message. Which party will take the lead in communicating will be determined case-by-case.

The points for attention for communication about various solutions are presented below.

4.1.1. The alternative medicinal product is authorised in the Netherlands with the same active substance and comparable strength and pharmaceutical form

This situation is comparable to generic substitution.

KNMP/LHV AHA information requirements:

- what alternatives are available?
- how long will the situation last?

Required time: two working days are required to coordinate reimbursement of the alternative with insurers and prepare communications for the community.
Dutch Association of Hospital Pharmacists information requirements: same as for the KNMP; issue of reimbursement is moot.

Patient federation and care provider information requirements: same as for the KNMP, but also wants to know how reimbursement will be organised (this is coordinated with insurers by the KNMP). KNMP/LHV AHA informs the Patient federation and care providers about this.

4.1.2 The alternative medicinal product is authorised in the Netherlands with the same active substance, but it does not have a comparable strength and/or pharmaceutical form, or
the alternative medicinal product is authorised in the Netherlands with the same active substance and a comparable strength and pharmaceutical form, but it is a medicinal product that requires additional attention where substitution is concerned.

If multiple alternatives exist, pharmacists and prescribers want to be involved in selecting the alternative.

This solution requires the pharmacist or prescriber to provide the patient with additional support and education, so pharmacists/prescribers need to be well-informed.

KNMP/LHV AHA information requirements:

- What alternatives are available?
- How long will the situation last?

Required time: one week is a realistic timeframe for coordinating what is a good alternative and preparing communications for the community. During this period, two working days are required to coordinate reimbursement of the alternative with insurers,

Dutch Association of Hospital Pharmacists information requirements: same as for the KNMP; issue of reimbursement is moot.

Care provider information requirements: same as for the KNMP/LHV AHA, including information about reimbursement.

Patient federation information requirements: if the alternative has been selected, immediately involve the Patient federation to prepare communication with members. One week is a realistic timeframe for this. Information about reimbursement is also important in this case. This is
coordinated with insurers by KNMP/LHV AHA, and the KNMP/LHV AHA subsequently informs the Patient federation.
Also consider using a support point for patients (e.g. National Health Care Report Centre).

### 4.1.3 The alternative medicinal product is authorised in the Netherlands with a different active substance

In this situation, prescribers will need to be consulted about selecting a good alternative. Additionally, the information described under 4.1.2 also applies here.

### 4.1.4 The alternative medicinal product is not authorised in the Netherlands. This is then based on section 3.17 or a (forwarded) pharmacy preparation.

If multiple alternatives exist, pharmacists and prescribers want to be involved in selecting the alternative. If the medicinal product contains a different active substance, discussion with prescribers about selecting a good alternative will be needed.

**KNMP/LHV AHA/prescriber information requirements:**

- What alternatives are available?
- Will a Dutch package leaflet be provided with the product by the supplier, or will the pharmacist need to provide it? (this is less of an issue for intramural medicinal products)
- How long will the situation last?
- How is this medicinal product reimbursed?
- How can the medicinal product be ordered/obtained? (preferably, the medicinal product should be available via regular wholesale supplier) and how quickly will this product be physically available in the pharmacy?

Timelines are comparable to those listed under 4.1.2.

### 4.1.5 An intervention is made in the treatment (specific target group, lower dose, shorter period of supply to a patient).

The impact will differ per case. Proper framing of the impact of the modified treatment for the patient must be part of the communication strategy. Good coordination with prescribers and pharmacists is required. However, the timelines and communications described under 4.1.2 still apply.
4.2 Completion

Every notification of a shortage must also be completed. If the shortage has been resolved, previously involved parties are informed.

5. Composition of the Operational Team

The following organisations/groups are represented in the Working Party on Medicinal Product Shortages

- Ministry of Health, Welfare and Sport
- IGZ
- MEB
- Health insurers: ZN
- Wholesale suppliers: BG Pharma
- Companies: Association for Innovative Medicinal Products in the Netherlands/Bogin/GLN
- Dispensing parties: KNMP, NVZA, LHV
- Patients: Patient federation/Consumentenbond (consumer protection agency)
- Prescribers: FMS/LHV/NHG

The Operational Team starts with MEB and IGZ, and they keep the Ministry of Health, Welfare and Sport appraised.

If no alternatives are authorised and available in the Netherlands, and no good solution is found together with the marketing authorisation holder, the Operational Team is expanded to include at least the companies and wholesale supplier. The umbrella organisations must also be expanded to include the VES (parallel import products).

Chapter 4.1 also describes when dispensing parties, practitioners and patients are involved in the Operational Team. As soon as the available alternative has been identified, health insurers and wholesale supplier are informed.
Appendix 3: Roadmap: routes

<table>
<thead>
<tr>
<th>Melding situatie</th>
<th>Notification situation</th>
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<td>Market share information</td>
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<td>Opschalen mogelijk?</td>
<td>Scaling up possible?</td>
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<tr>
<td>Firma stelt eisen</td>
<td>Company sets demands</td>
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<tr>
<td>Overleg met VWS</td>
<td>Consult with Ministry of Health, Welfare and Sport</td>
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<tr>
<td>Identiek product in andere lidstaat</td>
<td>Identical product in another member state</td>
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<tr>
<td>Herverdelen voorraden op EU-niveau</td>
<td>Redistribution of supplies at EU level</td>
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Summary:
- Alternatief geregistreerd in Nederland: Alternative authorised in the Netherlands
- Informatie marktaandeel: Market share information
- Opschalen mogelijk?: Scaling up possible?
- Firma stelt eisen: Company sets demands
- Overleg met VWS: Consult with Ministry of Health, Welfare and Sport
- Identiek product in andere lidstaat: Identical product in another member state
- Herverdelen voorraden op EU-niveau: Redistribution of supplies at EU level
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<td>Alternatief geregistreerd in EU</td>
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<td>Vergelijkbaar, maar niet identiek product</td>
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<td>Alternatieve API bron</td>
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<td>Etc.</td>
<td>Etc.</td>
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<tr>
<td>Beperking behandeling</td>
<td>Limit treatment</td>
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<tr>
<td>Minder hoog doseren</td>
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<td>Behandeling uitstellen</td>
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<td>Afleverafspraken</td>
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<td>Aleen specifieke patiënten groepen</td>
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<td>Voor kortere periode afleveren</td>
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<td>Herverdelen voorraden</td>
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