



EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems, medical products and innovation
Medical products: quality, safety, innovation

Summary of Responses to the Questionnaire on the Measures implemented in the Member States territories in the context of Article 81 of Directive 2001/83/EC

The questionnaire is linked to the call of the Council and the European Parliament to examine and monitor Article 81 of Directive 2001/83/EC of the pharmaceutical legislation, which introduces an obligation for continuous supply of medicinal products¹.

Article 81 of Directive 2001/83/EC:

With regard to the supply of medicinal products to pharmacists and persons authorised or entitled to supply medicinal products to the public, Member States shall not impose upon the holder of a distribution authorisation which has been granted by another Member State any obligation, in particular public service obligations, more stringent than those they impose on persons whom they have themselves authorised to engage in equivalent activities.

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

The arrangements for implementing this Article should, moreover, be justified on grounds of public health protection and be proportionate in relation to the objective of such protection, in compliance with the Treaty rules, particularly those concerning the free movement of goods and competition.

Responses have been received from 27 MS (AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LV, MT, NL, PL, PT, RO, SE, SI, SK, UK) and NO.

1. How is the obligation of continued supply transposed in your country as far as marketing authorisation holders (MAH) are concerned?

From the feedback received it appears that the obligation to ensure appropriate and continued supply has been transposed in a literally sense by the majority of the respondents (e.g. AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, IE, IT, LT, NL, PL, RO, UK).

Additional provisions, however, have been included in some countries:

- FI requires that the MAH ensures a constant availability of the product to wholesalers and pharmacies.
- In FR, appropriate measures to prevent and overcome supply difficulties are required to be in place and in case of shortages information must be provided to the authorities, hospital pharmacies, pharmacies, wholesalers and healthcare professionals, if needed.
- IT requires the MAHs to supply the pharmacies with the medicinal product unavailable in the national distribution network within 48 hours.
- DK, NL and PL require the MAH to provide, upon request, information about the amount of product that can be delivered to the market.

¹ https://ec.europa.eu/health/sites/health/files/files/committee/78meeting/pharm730_6ii_shortages_of_medicines.pdf
<http://www.europarl.europa.eu/sides/getDoc.do?type=REPORT&reference=A8-2017-0040&format=XML&language=EN>

- RO requires that the MAH ensures supplies equal to at least the average monthly turnover of the product over the past three months.
- In SE, there is a specific obligation on the MAHs to supply certain medicinal products subject to reimbursement. A MAH who also distributes medicinal products has an obligation to supply medicinal products to pharmacies as soon as possible.
- SK also places a specific obligation on the MAHs to supply medicinal products subject to reimbursement.

Some MS responses did not indicate that national legislation directly requires the MAH to ensure continued supply (e.g. CY, LV, MT, NO, SI) although this might be implied in some instances by the requirement to notify temporary or permanent supply interruptions to the authorities.

In NL, specific provisions have been included in the purchasing contracts between health insurers and MAH:

- 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.

2. **What are the responsibilities of wholesale distributors in your country stemming from the transposition of the obligation of continued supply (i.e. public service obligation)? Do you distinguish between full-line distributors and other distributors?**

(According to Directive 2001/83/EC, the public service obligation is "the obligation placed on wholesalers to guarantee permanently an adequate range of medicinal products to meet the requirements of a specific geographical area and to deliver the supplies requested within a very short time over the whole of the area in question.")

Responsibilities of wholesale distributors/ public service obligation

The majority of respondents indicate that wholesale distributors are obliged to ensure continued and adequate supply (e.g. AT, BE, BG, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LV, NL, MT, PL, PT, SE, SI, UK). The transposition of the distributors' responsibilities is linked to the transposition of the MAH obligations and hence in several instances the national legislation specifies "within the scope of their relevant/respective responsibilities"(e.g. AT, BE, ES, HR, IE, MT) or combines the responsibilities through the wording "in cooperation" or "in collaboration" with wholesale distributors (e.g. LT, PT).

In some instances the obligation specifies supply in quantities/time intervals adequate for the needs of patients (e.g. CZ, ES, PL) and refers to the needs of a specific geographic area (e.g. HR, PT, CY) and permanent assortment of products (e.g. IT).

Additional specifications have been implemented in some cases:

- Some respondents indicated also the maximum delivery time permitted e.g.: 48 hours for CZ, 12 working hours in IT, 24h in SE, 24 working hours in ES, 24-48h in NO. NO also may require delivery outside the opening hours of the pharmacies. SK requires a 24h delivery only for medicines subject to reimbursement.
- In CZ, the distributor has the right to request from the MAH a supply corresponding to the distributor's market share and the MAH is obliged to fulfil the request. The distributors are legally obliged to proceed in compliance with measures issued by the authorities for the purposes of safeguarding the availability of medicines.
- FR requires that the wholesalers should respect their distribution territory and public service obligation by holding stock to cover the usual needs of clients for minimum 2 weeks, delivering within 24 hours the orders received before Saturday 14:00, and participating in the weekend on-call duty to deliver orders within 8 hours.

- IE indicated an expectation by the authorities that the wholesaler has detailed procedures in place on the ways how appropriate and continued supplies are ensured and that these procedures have been demonstrated to be effective (this may include allocation quotas).
- Some respondents indicated that the wholesalers are obliged to notify the authorities of supply failure (e.g. in DK on every weekday before 12pm) and about the expected duration of the discontinuation (e.g. HU). Sometimes the wholesale distributors are also obliged to submit supply data and information so that the authorities can monitor the supply situation on the national market (e.g. LT).
- FI has separate legislation for importers of life-saving or essential medicines requiring the distributors to hold an obligatory surplus stock (mandatory reserve supply of 3-10 months sales calculated from previous year's sales); the reason for this law is the lack of manufacturers of essential medicines in Finland. There is compensation to the stockists defined in the Finnish legislation.
- RO requires that wholesalers ensure the public service obligation permanently by setting up insurance stocks equal to the average monthly sales for each drug in the list they distribute and honour any justified order received from the beneficiaries with whom they have contractual relationship.

Distinction between full-line distributors and other distributors

Most of the responses indicate that the national legislation does not distinguish between full-line and other distributors (e.g. AT, BG, CY, CZ, DK, EE, ES, FI, HR, IE, IT, LT, LV, NL, MT, NO, PL, PT, RO, SE, UK).

BE, DE, FR and SI make a distinction between full-line distributors (linked to the public service obligation) and other distributors, whereas SI distinguishes between full-line, contact-line and short-line distributors.

- BE legislation requires that the full-line distributors are at least obliged to permanently possess a stock allowing meeting the normal daily supply demand in their region of operation. The full-line distributors are obliged to make a commitment to deliver medicines to the entities authorised for distribution to the public and to take all necessary measures to ensure emergency deliveries within 24 hours of the order.
- In DE full-range wholesalers are obliged, within the framework of their responsibility, to guarantee a demand-oriented and continuous supply to the pharmacies with which they do business. The same obligation applies analogously to other types of wholesalers and their stock.
- FR requires that wholesalers should respect their distribution territory and public service obligation by holding stock to cover the usual needs of clients for minimum 2 weeks, delivering within 24 hours the orders received before Saturday 14:00, and participating in the weekend on-call duty to deliver orders within 8 hours. A distinction is made between full-line distributors and other distributors, because wholesalers are the owners of their stocks and consequently are subject to public service obligations as foreseen by the French Public Health Code. On the contrary, storage depositories are not the owner of the medicines; thus, they are not subject to the public service obligation.
- In SI, the public service obligation is very explicit for wholesalers. Wholesale distributors must guarantee a permanent and adequate range of medicinal products that may be marketed in accordance with the public service obligation of supply within a relatively short period of time, i.e. within 24 hours on weekdays or within a maximum of 72 hours at weekends and holidays after receipt of an order.

3. **What are the limits of their responsibilities in your country?**

The responses indicate that the limits of the responsibilities of MAHs and wholesale distributors are determined by the following:

- practical limits of availability from manufacturers or other wholesalers, e.g. if there is no API available, no medicinal product can be produced or supplied or in case of disruptions due to manufacturing problems and product suspension/withdrawal (e.g. AT, EE, FI, LV, RO, SE, PL);
- the responsibility of the wholesaler is limited by products they stock (e.g. NO);
- delivery time depends on the distance to the place of delivery (e.g. LV);
- MAHs are not subject to public service obligation which applies only to full-line wholesalers (e.g. FR);
- wholesale distributors do not have to be proactive and investigate other ways of supply (e.g. DK);
- the wholesale distributors' obligation to ensure continuous supply only applies to medicinal products subject to reimbursement or with a price agreement (e.g. LV, SK);
- wholesalers and manufacturers may apply for exemption from obligatory storages in some situations (e.g. FI).

4. **What are the responsibilities of manufacturing authorisation holders and how are they connected to the responsibilities of the marketing authorisation holder and the wholesale distributors? Is consultation with the authorities and notification of shortages obligatory?**

The responses to Question 4 varied considerably and are summarised and grouped by relevance below:

Responsibilities of manufacturing authorisation holders

In general, there are no specific responsibilities for manufacturers. However, in FI manufacturers are also required to hold obligatory stocks, if the medicinal products which they import or manufacture, are defined in the legislation of obligatory stocks.

Connection of the manufacturing authorisation holder's responsibilities to marketing authorisation holder's (MAH) responsibilities

DK, FR, LT, PL either require or expect a contract between the MAH and manufacturer (when these are different companies).

In EL, manufacturers should notify immediately the marketing authorisation holder (MAH) of any quality problem that may lead to product recall or abnormal availability of a product.

In ES, MAHs are required to have a prevention plan for supply problems if they report many disruptions of supply or shortages that affect to critical medicines.

In IE, both manufacturers and MAHs have obligations to ensure continued supply to patients, independently of each other, as the two actors are handled under separate national legislation. A single company may have obligations as a wholesaler, a manufacturer and a marketing authorisation holder under actor specific legislation.

Connection of the manufacturing authorisation holder's responsibilities to wholesale distributors' responsibilities

EE requires that manufacturers and wholesale distributors of medicinal products must ensure a continuous and sufficient choice of medicinal products and expedient delivery within the territory of Estonia.

In FI, HR, LT, UK manufacturers that supply their own or imported products are also considered as wholesalers and the same requirements apply as for wholesalers (including public service obligation).

FR requires that there is a contract between the MAH or the manufacturer and the storage depository.

In PL, manufacturing authorisation holders/marketing authorisation holders have legal obligation to deliver to wholesalers.

RO obliges the MAH to ensure that each product is distributed by at least 3 distributors.

Is consultation with the authorities and notification of shortages obligatory?

In some MS, the manufacturers are also required to notify in case of shortages (LV, NL, NO, PT). NO requires that national manufacturers report to the authorities while other manufacturers inform the MAH. PT requires manufacturing authorisation holders to immediately notify the authorities of any quality issue that might lead to a recall or might restrict the normal supply of medicinal products/IMPs.

HU moderates meetings between different members of the distribution chain in case of shortages.

5. Is there a specific definition of product supply disruption or shortage in your national legal order or other regulatory guidance? If yes, please describe it including a reference. Is it linked to a specific medicinal product² and to a specific territory³? Is it linked to the public service obligations referred to under questions 1 and 2?

The responses to Question 5 are summarised and grouped by relevance below:

Definition of product supply disruption or shortage in the national legal order or other regulatory guidance

Most of the respondents reported that there is no specific definition of supply disruption or shortage in their respective national legislation (e.g. AT, BG, BE, CY, CZ, DE, DK, EE, EL, ES, FI, HR, IE, IT, MT, NO, PL, SE, UK).

DE, DK, ES and SE reported to have definitions/classifications in their internal procedures.

In some MS, national legislation does not directly define shortages, but this is implied from the obligation to notify (HU, LV, NL, PT) or from the methodology for determining a sufficient stock of medicinal products (SK).

NL defines supply disruptions in the instructions for notifications to marketing authorisation holders and a shortage from a patient perspective in their regulatory guidance.

FR defines a product supply disruption as the incapacity for a pharmacy or a hospital pharmacy to dispense a medicinal product to a patient within 72 hours⁴. The origin of the product supply disruption could be a drug shortage or a disruption within the supply chain. Thus, the drug shortage is defined as the inability to manufacture a medicinal product while the disruption within the supply chain is defined as the lack of supply to pharmacies in the absence of drug shortage.

RO considers a decrease for seven consecutive days of stock at national level (for the category of drugs with the same substance), pharmaceutical form and concentration, under the average monthly turnover as a shortage alert situation.

SI defines a disruption in the supply of a medicinal product as a state of the market where business entities responsible for market supply in Slovenia fail to provide the required amounts of medicinal products at the appropriate time⁵. This definition applies to all entities of the distribution chain (manufacturers, MAHs, wholesalers and pharmacies).

² Do you assess the shortage in the light of a specific authorised medicinal product or a class of products

³ Do you assess the shortage in the light of the situation in a specific region affected or at national level

⁴ French Health Code (Article R. 5124-49-1)

⁵ Article 6 ZZdr-2, item No. 36

Definition linked to a specific medicinal product and to a specific territory

DE, FR reported that its definition is not linked to a specific medicinal product and a specific territory.

LV links its definition to a specific product and to the national territory.

In SI, a disruption in supply (a shortage) is technically treated on the product-level, however it can refer also to a group of products, and be treated as such in a rather general way. In terms of regional/geographic treatment, shortages are always treated on a national level in Slovenia, regardless if they occur only in a particular part of the country.

SK links the determination of a sufficient stock to products included in a reference group. A distinction of seasonal use is also made.

Definition linked to the public service obligations referred to under questions 1 and 2

DE, FR reported that its definition is not linked to the service public obligations referred to under question 1 and 2.

6. **Are there specific legal and/or other regulatory measures for critical or essential medicines (e.g. buffer stock)? If yes, do you have a definition of critical or essential medicines, do you use the WHO list of essential medicines or apply another solution? Please provide the definition and describe how you maintain and update the list of critical or essential medicines and describe any practical implementation issues.**

Specific legal and/or other regulatory measures for critical or essential medicines (e.g. buffer stock)

Several responses indicated that there is no specific legal or regulatory measures for critical or essential medicines (e.g. AT, BE, CY, CZ, DK, EE, EL, ES, LV, NL, MT, PL, SK). In EE, discussions with different stakeholders and governmental bodies are ongoing to clarify, if an initiative to introduce new legal measures for critical or essential medicines is necessary.

In BE, a decision tree is currently in a testing phase (till mid 2018). The aim of this decision tree is to detect critical supply problems quickly. By following the different steps of the decision tree one is able to decide if alternative medicines are available. If not, other solutions are sought. When the outcome shows that there is no alternative medicinal product available additional information about the supply problem is published. Flagging of shortages affecting critical or essential medicines is being considered.

DE has introduced as a basic requirement for the supply relevance of an essential active substance or combination of active substances. Medicinal products classified as critical in Germany contain essential active substances which are subject to special regulatory supervision due to an increased supply risk. Special monitoring by the authorities is required, in particular, where only one marketing authorisation holder (MAH), or only one manufacturer responsible for batch-release, or only one manufacturer of active substances is available.

FI has specific legislation in place in relation to e.g. life-saving or essential medicines (see also point 2).

FR has specific legal measures in its healthcare law for essential/critical medicines.

NO has a buffer stock arrangement in place. Similarly, SE has emergency preparedness stocks with certain antidotes and antivirals that are managed by the authorities in accordance with government decisions. Sweden does not have a national list of essential medicines; the lists are managed at a county level.

SI has legal measures in place for essential and indispensable medicines⁶.

⁶Article 17 Zzdr-2

Definition of critical or essential medicines

BE defines a medicine as critical or essential when there is no alternative treatment available. However, at this time there is no precise definition/description.

DE introduced a distinction between essential and critical medicines/active substances (see 6.1.)

ES has the following definitions in place:⁷

- **Essential medicinal product**: A medicinal product whose absence in the market may cause a problem of great care impact due to any of the following reasons:
 - o A medicinal product that has no therapeutic alternatives available in the market (therapeutic gap).
 - o A medicinal product that, despite having therapeutic alternatives available, accounts for a large share of the market and the alternatives are not able to cover the lack generated.
 - o A medicinal product whose absence, regardless of whether there are therapeutic alternatives available or not available in the market, has a high economic impact on the health system. (Therapeutic gap from the point of view of pharmaceutical provision).
- **Critical medicinal product**: A medicinal product identified with a potential risk of causing supply or shortage problems due to any of the following reasons:
 - o It is a medicinal product that has no available therapeutic alternatives
 - o It has a complex manufacturing process and/or only one supplier

FR definition: Critical medicines or therapeutic class of critical medicines are defined as medicines for which disruption of treatment is life-threatening or irreversibly progressive, or without which the patient could be severely harmed (short or mid-term) considering the potential evolution of the disease.⁸

IT, LV, NL, UK refer to the definition of critical medicinal product and the related criteria that were adopted by an EMA working group on shortages on 3 September 2013 and distinguish them from the list of essential medicines prepared by WHO.⁹

SI defines essential and indispensable medicinal products; **Essential medicinal products** are those that are, based on the latest knowledge in biomedical sciences as well as on the systemic definitions within the framework of national health priorities and taking account of the sustainability of public finances, considered indispensable for the provision of health care to people or animals and are placed on the list of essential medicinal products. **Indispensable medicinal products** are those that are not included in the list of essential medicinal products and for which a tertiary health care provider or an expanded expert panel for the relevant area establishes new scientific grounds based on which the authorities shall enter the products on the list of indispensable medicinal products.

Use of the WHO list of essential medicines or another solution

DE compiled a list of essential active substances based on proposals of medical specialists and the WHO list of essential medicines.

EE has made publicly available an overview of how many of the marketed medicinal products do not currently have any alternative treatment in Estonia (either they were the only medicine containing this active substance, because of the content of the active substance, or a special dosage form).

ES has compiled a list of essential medicines, based on previous shortages problems, which is not public. The list is based on the WHO list of essential medicines but additional criteria based on the definitions and past experience are also used.

⁷ AEMPS Strategy against shortages "Reflection paper on availability of medicines"

⁸ Article L. 5111-4 of the French public health code)

⁹ EMA/24304/2016, Criteria for classification of critical medicinal products for human and veterinary use Shortages due to GMP non-compliance/quality defects

In FI there is no specific definition for an essential medicine per se. The list of essential medicines to be stored is based on consultation of clinical experts. The list is updated and published once a year on the agency's homepage. The agency is committed to assess the need for updating the list of pharmaceutical substances every second year.

FR has developed a list of ATC classes and vaccines which are deemed as critical medicines. On this basis, the MAH should use the following criteria to identify the critical medicines for which a shortage prevention plan is needed:

- The absence of available alternatives in sufficient quantity on the French territory;
- The market share of the medicinal product in France and the market shares of the identified alternatives;
- The weaknesses in the manufacturing process of the product, e.g. the absence of alternate sites of manufacturing and/or packaging for raw materials, finished products, packaging articles; the complexity of these processes or those relative to the storage or to the transport of the product.

IT prepares a weekly report on medicines under shortage highlighting all situations where an alternative is not available on the Italian market

In MT, the Government Hospital has an online formulary list which includes essential medicinal products, vitamins, food supplements and borderline substances. Apart from the Government Hospital Formulary List, a specified Out Patient's Formulary list covering chronic conditions is also available. This list is intended for use by the Pharmacy Of Your Choice (POYC) scheme, and government pharmacies.

NO established its own list. There are two arrangements in Norway: one for general practice and another one for hospitals. For primary care the requirement of two months extra stock for use in general practice applies (wholesalers legislation). There is also an agreement between hospitals and wholesalers for supply of certain critical products. It is the responsibility of the hospitals to select the products on this list.¹⁰

PT published a notice containing a list of APIs in relation to which the pharmacies must inform the authorities, within 48 hours, of any lack of access to medicines experienced¹¹. This communication can be done by telephone or using a dedicated email address. This list of APIs was based on the WHO list of essential medicines and has not been updated since 2012 due to Portugal's stable profile of diseases' prevalence and incidence.

SI has a list of essential and indispensable medicinal products. In this list, essential medicinal products are identified by the common name, pharmaceutical form, strength and the method of prescribing and dispensing. On the proposal of the agency, the list of essential medicinal products is determined by the minister. Essential medicines and indispensable medicines may correspond to an officinal product which also may be marketed. The list of essential medicinal products and the list of indispensable medicinal products are published on the agency's website.¹²

7. Which other actions (not mentioned under questions 1 and 2 and not related to Article 23a) are the MAH, distributors, or pharmacies required to take when anticipating or experiencing product supply disruption? Which legal or regulatory measures are in place (e.g. supply continuity plan for the production, information obligations in the supply chain)?

No other actions than those referred to in points 1 and 2 or related to Article 23a of the Directive 2001/83/EC are required in AT, BE, CZ, DK, EE, HR, IE, IT, MT and NO.

Other responses indicate a wide range of legal and/or regulatory measures for the prevention or management of shortages:

¹⁰ https://lovdata.no/dokument/SF/forskrift/1993-12-21-1219/KAPITTEL_10#KAPITTEL_10

¹¹ Informative Notice number. 235/CD/8.1.6, of 21th November of 2012

¹² <http://www.jazmp.si/humana-zdravila/podatki-o-zdravilih/zdravila-na-trgu/>

BG requires that with termination of the sales of a medicinal product from the Positive Medicines List and where within the frame of the relevant INN there is no other authorised medicinal product, the MAH notifies in writing the Ministry of Health and the National Council of Medicinal Products Prices and Reimbursement not later than 18 months prior to the date of discontinuation of the sales. Prior to the discontinuation of the sales, the MAH is obliged to secure sufficient quantities of the respective medicinal product for satisfying the health needs. When the authorities receive a signal of termination of sales of a medicinal product (with the exception of cases under Article 23a), the BDA performs a check within 30 days. While performing the check, the BDA may request information from the MAH on termination of the sales of the concrete medicinal product, as well as from the wholesalers about the available quantities of the products. Information obligations in the supply chain and inspections on site are applied.

In CY the authorities are informed of any drug shortages and based on the current use and availability of alternatives, communicate with the MAH to ensure stock controlling and to avoid serious disruptions of the market supply. Additionally, the Procurement Department of the Ministry of Health may procure alternative products or products from other markets in order to respond to emergencies.

DE requires that MAHs inform hospitals in case of known shortages of prescription medicines for inpatient treatment. MAHs report supply disruptions on a voluntary basis to the German authorities if:

- the supply shortage relates to marketed medicinal products of essential active substances for which three or less MAH, manufacturers responsible for batch-release, or manufacturers of active substances are available;
- the market share of the medicinal product affected by the supply disruption is more than 25%;
- supply shortage has already been reported in the past for the concerned active substances.

EL requires the MAH to inform the authorities of any marketing cessation (permanent or temporary) or shortage. This information should be notified at least 3 months before cessation of the product. In addition, product supply shortages are also notified by healthcare professionals or patients. The Greek authorities evaluate the impact of the shortage on public health.

In ES other actions which are required from marketing authorisation holders/distributors in case of a supply disruption are:

- Obtaining units of medicinal products in supply shortage, labelled in other languages or with expiry date shorter than 6 months, to be authorised by the Spanish Agency of Medicinal Products and Medicine Devices, allowing their placing on the market under exceptional circumstances. These units are only to be commercialised to hospitals (to MAH).
- Importing medicinal products with the same composition as the affected medicinal product, from other countries (foreign medicinal product) (to MAH).
- Revision of supply chain of the units recently distributed and cancelation of the exports, when applicable (to MAH and distributors).
- Restriction of the supply to allocate the units for indications without another therapeutic alternative, to extend the duration of the available units (to MAH).

FI requires that wholesalers inform pharmacies directly or via their full-line distributors of any disruptions to their normal availability of medicinal products and that pharmacies hold stocks as follows: “The amount of medicinal products, the equipment and supplies for administering medicinal products, and the dressings kept by a pharmacy must correspond to its usual customer needs.”

FR adopted specific legal measures for critical medicines or therapeutic class of critical medicines for which the MAH should develop and implement prevention/management plans in order to prevent and/or mitigate impact on patients, to warn of (prevent) any drug shortage. In this context, MAH should declare to the French agency the list of their medicines for which prevention/mitigation plans are implemented. The list of the critical medicines for which prevention/mitigation plans are set up, should be mentioned in the site master file. These documents should be available to the authorities on demand. The prevention/mitigation plans are based on the risk analysis of the production and distribution cycle of the related medicinal product. These plans should anticipate measures to be implemented according to the weaknesses identified and the market shares of the related product: e.g.

security stocks of products, alternate production sites and also identification of alternatives. Moreover, the MAH should inform the French authorities of any shortage/risk of shortage of critical medicines. When a MAH anticipates, notices or is informed about a situation of drug shortage of a critical medicine, it should inform immediately the agency and specify the lead-time for shortage, the available stocks, the deadline for the end of shortage and (if necessary) the identification of alternatives. In case of critical medicines, the measures described in the shortage prevention/mitigation plan should also be provided. The MAH should implement, with the agreement of the agency, alternative solutions to deal with the situation and for critical medicines the measures described in the prevention/mitigation plan and have to inform the healthcare professionals.

IE has implemented an expectation for wholesalers that are the same legal entity and co-located with a retail pharmacy business, where the predominant business activity of the wholesale function is to parallel trade medicines out of Ireland. The expectation is that the wholesale entity will establish and use a dedicated account with its supplier for the purposes of procuring medicines for onward wholesale distribution, including parallel trading.

LT foresees the legal possibility of supplying unauthorised medicinal products: the named medicinal products (according to Article 5 of Directive 2001/83/EC), unauthorised relevant medicinal products (according to Article 126a of Directive 2001/83/EC), and unauthorised products in emergencies. Lithuanian legislation also establishes the possibility to supply authorised medicinal products in foreign language packages (according to Article 63 of Directive 2001/83/EC). Lithuania, Latvia, Estonia have signed an agreement on use of the common Baltic packages, which facilitates the authorisation of medicinal products in these countries.

LV links additional obligations (*not detailed in the response*) to the reimbursement of medicinal products.

NO expects that wholesalers avoid exports of medicinal products that would create shortages and applies a crises management regulation in extreme cases (high number of patients where lack of medication will have severe consequences), but considers this measure unsuitable for ordinary supply disruptions.

PT has created an online platform for the notification and management of the shortage (“*SIATS platform*”) and established a legal mechanism to monitor the exportation/EU distribution of medicinal products: the *ex-ante* notification list. If a given medicine is included in the *ex-ante* notification list, and its supply to the national market is compromised, the authorities may temporarily ban the export or the distribution of that medicine to other EU countries. PT uses the following methodology to assess the notified shortages:

- Assessment of the length of the shortage, market share of the product (sales declared) and evident alternative medicines (e.g. other brand with the same API available) – performed by INFARMED, I.P.;
- Preliminary classification of the shortage regarding the impact on national market, as high, medium or low – performed by INFARMED, I.P.;
- Assessment of available alternative medicines (asking clinical experts’ opinion), if the shortage is considered of high or medium impact – performed by INFARMED, I.P.;
- Upgrade of preliminary classification, if applicable (existence of alternatives) – performed by INFARMED, I.P.;
- Preparation of a mitigation plan when the impact of the shortage on the national market is considered high or medium – performed by the MAH.

RO has put in place a dedicated an email address and a website platform where pharmacists or patients can notify the absence of a medicine from the market. The authorities verify the notifications and take appropriate measures.

SE requires agreements between stakeholders (MA-holder, distributors and pharmacies) that describe how each stakeholder should handle such a situation. There are for example rules for information obligations in the supply chain and the industry is committed to good accessibility of medicinal products.

In SI, pharmacies are obliged to perform the service of delivering the product to the purchasing party (individual on the outpatient basis, corporate on inpatient basis). Combined with the public service obligation from wholesalers, this provides a strong demand-side mechanism for assurance of the product when prescribed in an out-patient or in-patient setting.

In SK, wholesalers can export a classified medicinal product only with the agreement of the MAH of the classified medicinal product. The classified medicinal product must be delivered to the pharmacy within 48 hours from order.

UK has developed voluntary joint regulator-industry best practice guidelines that give advice to companies on what to do in the event of a shortage.¹³ This guidance recommends that companies communicate with the authorities as soon as possible about impending shortages that are likely to have an impact on patient care. This allows consideration of the available options for continued supply, which might include expediting regulatory procedures, commissioning clinical advice if required or identifying alternative sources of supply. The guidance also advises companies to consider whether/how best to communicate a supply problem to the National Health Service. In some cases, for example, the company will send a letter to affected clinicians and pharmacists, while in others, a note in the pharmaceutical/ trade press might be sufficient. In most cases, companies alert the wholesalers and other customers when a product is unavailable. Many pharmaceutical companies also operate their own out of stock portal on their company website that customers can subscribe too. The UK authorities recognise the need to have a central portal or webpage available about national medicine shortages and it is working with the National Health Service to develop and manage a nationally available website for medicines shortages information which should contain up to date information on shortages, their duration and recommended action where available.

8. Article 23a of Directive 2001/83/EC obliges the marketing authorisation holder to notify the authority if a product ceases to be placed on the market even temporarily. Do you make this information available to the distributors or pharmacies? Is there any other compulsory reporting of interruption of supply to the NCA, to distributors or pharmacies or to patients? Is this information publicly available? Are there penalties for non-compliance?

The responses to Question 8 are summarised and grouped by relevance below:

Do you make this information available to the distributors or pharmacies? Is there any other compulsory reporting of interruption of supply to the NCA, to distributors or pharmacies or to patients?

The responses indicate varying practices and requirements of reporting and information sharing.

The authorities in AT do not make this information available to distributors or pharmacies, however the MAH shares this information with distributors and pharmacies, hence they know if a product ceases to be placed on the market. The MAH is obliged to notify the agency of shortages linked to quality defects.

BE has reported that a notification tool has been made available to communicate changes in the commercialisation status of a medicine (start or stop of commercialisation, temporary unavailability or return on the market). All notified data are introduced in the national database of medicinal products authorised in Belgium. A new platform will be developed in 2018. This platform will facilitate the notification of the commercialisation/supply problems by the marketing authorisation holder and will automatically update the information in the national database. Furthermore an exchange of information will be possible between pharmacists/distributors and marketing authorisation holders.

DE does not publish the Article 23a notifications. In case of unforeseen shortages the MAH is required to notify the authorities without delay, while for planned supply interruption the notification is required 6 months in advance.

¹³<https://www.gov.uk/government/publications/notification-and-management-of-medicines-shortages-abpi>
<https://www.gov.uk/government/publications/notification-and-management-of-medicines-shortages-bgma>

In CY, the authorities may instruct the MAH to notify a shortage to pharmacies.

EE publishes selected information about a shortage for pharmacies, distributors and other stakeholders.

In FI, reporting of this information is compulsory.

FR requires that appropriate measures to prevent and overcome supply difficulties are in place. In case of shortage, information should be provided to pharmacies, hospital pharmacies, wholesalers and healthcare professionals if needed. Moreover, the firm that is responsible for marketing of the medicinal product in France should implement permanent emergency call centres (or an equivalent system) to allow direct contact with pharmacies and wholesalers. The emergency call numbers should be available for healthcare professionals.

NO makes this information available to distributors or pharmacies.

In PL, the public authorities do not make this information available to wholesalers or pharmacies.

SI publishes related information within 5 working days. MAHs, parallel distributors and wholesalers are obliged, at the request of the authorities, to provide data on sales volumes in Slovenia. Business entities that carry out pharmacy services or are engaged in the retail marketing of medicinal products in specialised stores shall submit to the authorities information on purchasing and dispensing of medicinal products. Health care service providers shall submit to the Slovenian authorities information on the purchase and consumption of medicinal products. Data on the volume of the sales, purchase, dispensing and consumption of medicinal products shall include the quantity of individual medicinal products and their buying and selling values for a specified period of time. The detailed requirements, manner, frequency and periods for data reporting and data models for communication and data reporting are laid down by the authorities. There is one single form that is adapted for reporting of various events and provides means for explanation and justification of the MAH's action, together with a request to assess the impact of its action (i.e. cessation of marketing) on public health. The form 281-04 (in Slovenian only) is available on JAZMP website.¹⁴

UK requires, in addition to the provisions of Art.23a, that MAHs notify their intention not to apply for a renewal of the marketing authorisation or to withdraw the product from the market in a third country (whether temporarily or permanently) and the action is based on any of the grounds set out in Article 116 or 117(1) of Directive 2001/83/EC.

Is this information publicly available?

The majority of respondents indicate that they publish information related to supply interruptions; however, the type and extent of this information varies. In general, this information is available at NCA's websites. Additional information is published in some cases:

ES also publishes information on available therapeutic alternatives, if the product will be imported or if supply is restricted to hospitals). In addition the Spanish Agency publishes informative notes on their webpage when a shortage of a medicinal product has an important impact on public health, or specific guidance for healthcare professionals or patients is needed.

Additionally, in HU, the public and the healthcare professionals are provided with information via newsletter, e-mail and phone.

In NO, specific shortage situations are published as news with advice to doctors, pharmacies and patients. Alerts to doctors are also implemented in the "Electronic Patient Journal" systems providing instant information about a specific medicine package (strength) at the point of prescribing and through the Norwegian Pharmaceutical Product Compendium.¹⁵ For patients, an app has been released where patients can register their medicines allowing them to access and receive relevant information (as alerts about shortages and deregistrations).

¹⁴ http://www.jazmp.si/fileadmin/datoteka/obrazci/SFE/Obr_281-04.docx

¹⁵ See red box on webpage <https://www.felleskatalogen.no/medisin/>

In PT information on medicine shortages notified by the MAHs on an electronic platform is accessible to prescribers through a link to prescription software allowing them to be informed in advance about the availability of a medicine.

Are there penalties for non-compliance?

Most respondents indicate that the national legislation foresees certain sanctions for non-compliance; these range from revocation of licences to financial penalties in varying amounts.

BG has no specific provision for imposing a fine on the MAH who fails to fulfill this obligation. However, the common fine for infringement of the relevant legislation is BGN 3,000 to 9,000.

CY foresees an administrative fine up to 34,000 € for failure to comply with the obligations set out in article 23a of the Directive 2001/83/EC (Section 14 of the National Legislation).

Since 2011, CZ has imposed financial penalties on MAHs in 99 cases of non-compliance (of which 94 are legally valid), in total amount of 2,651,000 CZK.

ES has penalties for non-compliance in its legislation. There are three very serious penalties and fines up to 1 million €.

In FI there are certain possibilities of prohibitions and revocations to the license holders if the conditions for granting the marketing authorisations no longer exist or requirements concerning manufacture or import are no longer met as required in the pharmaceutical legislation. However, so far no penalties have been imposed in case of not reporting as required.

FR applies penalties in case of non-compliance. These sanctions can be administrative measures or fines as mentioned in question 11.

HR foresees a fine between HRK 100,000 and HRK 150,000 for failing to act in accordance with the provisions of its pharmaceutical legislation.

In PT if an MAH does not comply with its obligations to electronically notify the authorities of shortages (if the notification isn't made at all or if the shortage is reported with delay), a warning can be issued or legal action against the MAH initiated if the noncompliance is recurrent.

LV applies penalties in this context.

RO applies penalties for not notify an interruption of supply to the MAH and the distributors and pharmacies have to inform the authorities if a justified order is not honoured.

SK foresees penalties between 500 € and 25,000 €.

In the UK a breach of Article 23a by the MAH is a criminal offence.

AT, DE, EE, NO do not impose penalties for non-compliance.

9. **Do you have any specific export restrictions in place to mitigate the shortage or the risk of shortage of medicines? If yes, what is their precise scope and what criteria are they based on? (e.g. prior notification for shipments within a certain timeline, dynamic list of products...)**

- a) **Do they apply in the same way for the exports to other EU Member States and to third countries?**
- b) **Are they based on generally applicable measures only¹⁶ or also on individual decisions of the state authorities¹⁷?**
- c) **Are substitutable medicinal products/therapies taken into account in such export restrictions?**
- d) **Are such export restrictions considered as part of transposition of the public service obligations under Article 81?**
- e) **What kind of information do you publish regarding the specific export restrictions taken?**

There are no specific export restrictions in relation to shortages in AT, BE, BG, CY, DE, DK, HR, IE, IT, LV, MT, NL, NO, SE, SI and UK.

However indirect measures with potentially equivalent effect have been introduced in some cases, such as SI, where there are explicit public service obligation provisions in place which act as a deterrent to the business policies of wholesalers that would lead to the exhaustion of the national markets.

Export restriction measures in the context of shortages exist in CZ, EE, EL, ES, FI, FR, HU, PL, PT, RO and SK.

a) Do they apply in the same way for the exports to other EU Member States and to third countries?

Yes: CZ, EE, EL, FI, FR, PL, PT, SK.

b) Are they based on generally applicable measures only or also on individual decisions of the state authorities?

The responses indicate that both general and/or individual measures may be taken.

c) Are substitutable medicinal products/therapies taken into account in such export restrictions?

Yes: CZ, EE, EL, ES, FI, FR, PT

No: SK

d) Are such export restrictions considered as part of transposition of the public service obligations under Article 81?

Yes: CZ, EE, ES, FI, FR, PT, SK

No: EL

e) What kind of information do you publish regarding the specific export restrictions taken?

The responses indicate that the most common information published is a list of specific medicinal products (e.g. with current availability problems or mandatory reserves).

10. **How are you determining and monitoring the shortage situation (e.g. by comparing supply and consumption data) for a particular medicinal product?**

a) **Is this monitoring linked to the export restrictions referred to in question 8?**

¹⁶ e.g. general ban for all exports applicable for all economic operators

¹⁷ e.g. individual decision to block the export for an individual economic operator (decision on case by case basis)

b) **Do you plan using, for the purpose of monitoring the data gathered, the secure repository system developed in the scope of Commission Delegated Regulation (EU) 2016/161 of 2 October 2015?**

The responses indicate that the most common practices involve contacts with the industry, monitoring of supply and consumption data and impact analyses (e.g. availability and stocks of alternative products). Monitoring can take place through electronic information systems/platforms crosslinking supply problems with export notifications. More than half of the respondents is considering the use of the EU secure repository system.

a) Is this monitoring linked to the export restrictions referred to in question 8?

Yes: CZ, EE, EL, ES, FI, PL

No: BE, CY, DE, FR, LT, NO, RO, SI

EE looks at the import and export history of the medicinal product, and if it has been exported recently or has the potential to be exported, an export restriction is considered.

FI makes its decisions based on monitoring of supply and consumption data.

b) **Do you plan using, for the purpose of monitoring the data gathered, the secure repository system developed in the scope of Commission Delegated Regulation (EU) 2016/161 of 2 October 2015?**

Yes: AT, CZ, EE, EL, ES, HR, IT, LV, SI

Under consideration: BE, CY, FR, LT, MT, PL, PT, RO

No: DE, FI, IE, NL, NO, SE, UK

11. **Are there specific penalties for interruption of supply/shortages? (e.g. suspension of distribution authorisation or marketing authorisation, fines for export or shipment of medicines to other Member States in case of shortages)? If yes, did you impose sanctions during the last 10 years and have the penalties for shortage resulted in reluctance from the MAH to inform you about shortages, or in deregistration of the medicinal product?**

The responses indicate that most authorities foresee sanctions (administrative or financial penalties); however, the majority of respondents have not applied them in the context of shortages in the last 10 years. No reluctance from the MAH to inform the authorities about shortages, or deregistration of the medicinal product as a consequence of specific sanctions in the context of supply interruption has been reported.

In CY, the national legislation provides for the imposition of an administrative fine up to 34,000 € for the failure to comply with the obligation to notify any disruptions/shortages in supply. No fines however have been imposed the past 10 years with regard to this obligation.

In CZ the MAHs can be fined up to the 20,000,000 CZK if they fail to fulfil their obligations; no sanctions in the context of Art. 23a of Directive 2001/83/EC were imposed in the past 10 years. CZ has imposed penalties on distributors in three cases of non-compliance with the prohibition of export in case of shortages (1.5 million CZK); one case is currently being reassessed (400,000 CZK) following an appeal filed by the company.

EE can fine wholesalers for infringing an export ban under the Code of Misdemeanour Procedure.¹⁸

EL has legal provisions for penalties for insufficient coverage of patients' needs.

ES has established penalties for MAH that stop the distribution of a medicinal product since it can only be suspended under exceptional conditions adequately justified once the authorization of the Spanish agency is issued. There are also specific penalties for exporting medicines when this activity

¹⁸ <https://www.riigiteataja.ee/en/eli/513072017004/consolide>

has been forbidden by the agency. ES imposed sanctions in the last 5 years on companies that did not notify supply disruptions. Nowadays, those companies report regularly its supply disruptions.

In FI there are certain possibilities of prohibition and revocation of licences if the conditions for granting the marketing authorisations no longer exist or requirements concerning manufacture of import are no longer met as required by the pharmaceutical legislation. However, so far no penalties have been imposed in case of not reporting as required.

FR foresees penalties for interruption of supply/shortages or risk of supply. There are many specific penalties (administrative or financial) for infringement of certain obligations, including the non-reporting of interruption of supply by the MAH to the authorities (ANSM) or the non-compliance with the public services obligations by the wholesalers. For example, when an inspection reveals that the activity of a wholesaler can lead to shortages (e.g. export of medicines that were intended to the French market, or failure to comply with the public service obligations), the ANSM can impose administrative sanctions like injunctions, or suspensions of the distribution authorisation. ANSM can impose financial penalties too. The amount of the penalty will not exceed 10 % of the firm's France turnover in the preceding business year, but limited to 1 million €. During the last 10 years, the following sanctions were taken against wholesalers following deficiencies in public service obligations/risk of shortages:

- nine injunctions (warning letters prior to 2014),
- six suspensions of the authorisation, and
- two financial penalty procedures have been initiated.

HR foresees fines for failing to act in accordance with the obligation of continued supply and failing to notify the authorities about shortage/supply disruption (see also answer to question 8). The Croatian authorities did not impose any sanctions during the last 10 years because of reluctance from the MAH to inform about a shortage. In addition to the fines, the "sunset clause" provision applies if a medicinal product has not been on the market for three consecutive years.

HU imposes penalties (fines) if it is proven that the MAH or wholesaler violated his obligation to supply.

IE only applies general penalties for the non-compliance with legislation by manufacturers, wholesalers and marketing authorisation holders. There are no specific penalties or fines for parallel trade relating to shortages. No sanctions have been imposed on marketing authorisation holders thus far and, given the relatively small size of the Irish market, IE feels that it may not address the issue of ensuring continued supply to Irish patients.

In IT, in case of violation of the Public Service Obligation or GDP, the distributor may be sanctioned and its authorization suspended or revoked; no other specific sanctions (fines, MA suspensions etc.) are foreseen with respect to the Marketing Authorization Holders.

LT authorities have the right to write the Protocol of Administrative Offences according to the Code of administrative offences in case a MAH does not perform its obligations. The protocol is submitted to the Administrative Court and the court takes a decision on the imposition of penalties. The Lithuanian agency has not issued any protocols on the basis of supply disruptions for the entire period.

NL applies penalties for violation of the MAH commitment to supply wholesale distributors and pharmacies and for untimely notification of expected shortages (currently 45,000-150,000€).

PT foresees fines between 2,000€ and 15% of the responsible person's turnover or 180,000€, depending on whichever is lower, for wholesalers or MAHs that don't comply with the obligation of supply the geographic relevant market, for MAHs that don't comply with the obligation to notify a shortage or for wholesalers that don't comply with the obligation to notify exportation in the terms explained in question 9. In the last 10 years, no fines were imposed in the context of non-compliance with shortage notification requirements, but regarding other non-compliances a total of 232 administrative offence processes were installed.

SE can revoke the wholesale license if the wholesaler fails to deliver medicinal products to pharmacies. There are no specific penalties for interruption of supply/shortages except in the cases

related to the obligation to supply reimbursable products (fines between 5,000 – 10,000,000 SEK). One case of a fine for the interruption of supply has been reported (20,000 SEK).

SI foresees penalties and has detailed legal provisions in place for their application. The legislation distinguishes between minor and major offences. The sanctions are imposed as fines for the legal entity (e.g. an economic operator), responsible person of the legal entity, and an individual. Examples of offences are: failure to communicate certain data, failure to fulfil the public service obligations and failure to fulfil the obligations of wholesalers. The fines range from 800 to 4,000 € for minor offences and from 8,000 to 120,000 € for major offences.

SK also applies financial penalties.

In the UK penalties exist in the pharmaceutical legislation for non-compliance with the legal provisions. Sanctions have not been applied to MAHs to date and MAHs continue to notify medicines shortages.

AT, BG, DE, DK, EE, IE, LV, NO have no specific sanctions for interruption of supply.

12. In the case of a MAH informing you of its plans to discontinue the marketing of a medicinal product (deregistration), where no other alternative is available, what actions are taken? Is there a dialogue with the MAH, concerning the consequences of the shortage?

Most respondents indicate that in case of deregistration/shortage a dialogue with the MAH is initiated.

PT has a dedicated working group dealing with the assessment of impact of supply discontinuation and engages in discussions with the MAH in order to minimise the impact of deregistration/shortages.

On the other hand, CZ does not engage in a dialogue with MAHs in case of deregistration.

Measures implemented in this context may include, among others:

- Shortage impact and substitution assessment (indicated by most of respondents).
- In some MS, the MAH should provide with information about therapeutic alternatives (ES, SI)
- In FR, essential medicinal products cannot be withdrawn from the market until an alternative solution has been identified.
- Stock monitoring: EL checks the potential alternatives stocks belonging to the same therapeutic category. The Greek authorities contact pharmaceutical companies, marketing authorisation holders of alternative medicinal products in order to communicate the problem and ask for potential increase of production and product stock).
- Notification of cessation at least one year in advance for essential medicines (FR).
- Special/exceptional import and manufacturing authorisations (CZ, EE, EL, ES, IT, LV, LT, NO, PT, RO).
- Fee reductions: providing some benefits e.g. fee reduction for the MAHs of certain, essentially important products with low sale data is under discussion in HU.
- Information to different actors in the supply chain and healthcare professionals (DK, EL, HR).

13. Can you describe some real life examples on how to act on shortage of essential medicinal products, in order to minimize the consequences of the shortage? What has worked, and what has not worked? Please share you experience.

[Answers removed due to their commercially sensitive nature.]