

01 July 2019
EMA/674304/2018

Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)

1. Introduction

This document provides guidance to marketing authorisation holders (MAHs) for reporting of shortages of medicinal products in the Union (EEA), based on a common EU definition of shortage. It does not cover any other availability issue such as withdrawals of marketing authorisations.

An essential element to a harmonised approach for reporting and managing shortages is the use of a harmonised definition of a shortage. The lack of a common definition has meant that the detection and coordination of the management of shortages in the Union (EEA) has been inconsistent. The differences in the reporting requirements of shortages also meant that comparisons across countries were not possible. This guidance which is based on a common definition agreed by all stakeholders, gives recommendations to facilitate the detection and reporting from marketing authorisation holders to competent authorities about impending shortages. Early notification to competent authorities is a key aspect in the prevention or mitigation of a shortage by allowing sufficient time to make contingency arrangements where necessary.

The guidance will address the following areas:

- *What is a shortage?*
- *What issues should be reported by MAHs?*
- *Who is responsible for monitoring supply and reporting shortages?*
- *When should a notification be made?*
- *Who should be notified?*
- *What information should be included in notifications?*



2. What is a shortage?

For the purpose of notification and detection of shortages by MAHs, the following definition, agreed by EMA, HMA and stakeholders, should be used:

'A shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level'.

where:

- a **'shortage'** as defined, allows for identification of current, impending or anticipated disruption of supply of a medicinal product.
- **'medicinal product'** as described in Article 1(2) of Directive 2001/83/EC and Article 1(2) of Directive 2001/82/EC. Medicinal products which contain the same active substance presented in different pharmaceutical forms and/or strengths and, when required by the national competent authority, pack sizes, are seen as individual unique medicinal products. The above definition applies to marketed human and veterinary medicines (not inclusive of medicines supplied on named patient basis or medicines supplied for compassionate use).
- **'supply'** refers to the total volume of stock of the individual medicinal product that is placed on the market by the Marketing Authorisation Holder.
- **'demand'** relates to the request for a medicinal product by a healthcare professional, veterinarian or patient in response to a clinical need. For demand to be satisfactorily met, the medicinal product will need to be acquired in time and sufficient quantity to allow continuity of best care of patients/animals. Wholesalers are usually a key supply link between MAHs and the users of medicines, and in those cases, in order to estimate demand, the quantity requested in wholesale orders should be considered.
- **'national level'** refers to the situation in a specific country, i.e. if there is insufficient supply of a medicine to meet the demands of the country overall. Logistic -related issues leading to regional supply disruption of a medicinal product e.g. delivery difficulties, national redistribution of stock, are a short term and localised problem and should not be taken into account.

3. What issues should be reported by MAHs?

Based on the above definition and irrespective of the clinical importance of a medicine, the following issues should be reported:

- All shortages which are currently affecting one or more EU member states;
- All impending/anticipated shortages which are expected to affect one or more EU member states.

The above includes all current and impending shortages which have or will occur due to regulatory issues, quality defects and/or any other causes; these include, but are not limited to GMP/GDP issues, batch failures and medicine product recalls.

4. Who is responsible for monitoring supply and reporting shortages?

Article 81 of Directive 2001/83/EC states that MAHs, and their distributors, within the limits of their responsibilities, should ensure appropriate and continued supplies to pharmacies and persons authorised or entitled to supply medicinal products so that the needs of patients in the Member State in question are met.

Furthermore, article 23a, 2nd paragraph of Directive 2001/83/EC and article 27a, 2nd paragraph of Directive 2001/82/EC state that if the product ceases to be placed on the market of a Member State, either temporarily or permanently, the marketing authorisation holder shall notify the competent authority of that Member State. Such notification shall, other than in exceptional circumstances, be made no less than two months before the interruption in the placing on the market of the product.

The "*Paper on the obligation of continuous supply to tackle the problem of shortages of medicines*", which was agreed by the Ad-hoc technical meeting under the Pharmaceutical Committee on shortages of medicines on 25 May 2018, provides clarification on the responsibilities of the MAHs and wholesale distributors. The limits of the responsibilities of marketing authorisation holders and wholesale distributors should be evaluated on a case-by-case basis by the Member States. Further explanation can be found in the relevant paper.

In order to be able to notify any interruption of supply to competent authorities, MAHs must continuously monitor the supply and demand situation of their medicinal products and have an open and continuous communication with all their operators in the supply chain, such as manufacturers and wholesalers. Early communication of relevant information is essential in handling shortages.

The MAH should also be particularly vigilant where it markets medicines for which no or only limited alternatives are available, and where interruption of supply will result in a potential risk to public health (e.g. clinically important medicines) and / or animal health and welfare. For those products, competent authorities may require marketing authorisation holders to develop a shortage prevention plan, as part of their obligation to ensure continuous supply.

The reasons for shortages are multifaceted and therefore, solutions require the co-ordinated involvement of all stakeholders across the supply chain. In some cases, more general issues (e.g. temperature excursions) at some operators (e.g. wholesalers and manufacturers) could result in a shortage impacting more than one product. Consequently, operators are expected to monitor the supply situation and report any relevant information to the MAH(s). These issues can, depending on national provisions, also be reported to the competent authority independently of the MAH.

MAHs have oversight of the supply of their medicines nationally and globally. They can therefore continually align demand with supply as well as understand the impact of a given shortage on patients and prepare an appropriate response. MAH oversight is also supported by other actors in the supply chain, who themselves may be able to monitor and detect 'signals' of shortages. An example of this is where a single manufacturer is contracted to produce medicinal products or active substances for a number of MAHs. The impact of a manufacturing issue in this case could extend beyond one specific product and it is important to monitor these signals. All operators are expected to monitor for signals. Signals may also come from community pharmacies, hospital pharmacies, retailers, healthcare professionals/veterinarians, patient groups and animal owners.

MAHs are in the best position to assess relevant information, as they have visibility of their stock, both national and global, taking into account foreseen shipments from their manufacturers. Following assessment of a signal and establishment that national supply cannot meet demand, a shortage – impending or anticipated- is confirmed. MAHs should report all current or impending/anticipated medicine shortages, regardless of the perceived medicinal product’s clinical importance and availability of alternative medicines.

MAHs and operators of the supply chain are expected to develop and maintain resilience in the supply chain by:

- regularly assessing supply information provided by their manufacturers and suppliers;
- regularly assessing market needs based on information provided by wholesale distributors, community pharmacies, hospital pharmacies, retailers, healthcare professionals/veterinarians or patient groups;
- developing shortage prevention and response plans.

For this purpose, MAHs are advised to utilise relevant guidance developed by professional organisations (e.g. ISPE Drug Shortages Prevention Plan, PDA Risk-Based Approach for Prevention and Management of Drug Shortages, PDA Technical Report 68).

5. When should a notification be made?

MAHs should notify the relevant EU competent authorities of any supply situation that meets the criteria outlined in section 3.

Although EU legislation requires the notification to be made no less than 2 months before the interruption in the placing on the market of the product, MAHs should notify the authorities as early as possible, as soon the shortage or the impending/anticipated shortage is confirmed. In addition there may be national reporting timeframes that should be taken into account.

Timely notification allows for early triaging, assessment and co-ordination of the medicine shortage. Early shortage notification allows for better management of the shortage by the competent authority and stakeholders and allows the competent authority to have time to validate the mitigation plan proposed by the MAHs and/or to collaborate with the MAHs and all the stakeholders (manufacturers, wholesale distributors, community pharmacies, hospital pharmacies, retailers, healthcare professionals/veterinarians or patient groups) in order to resolve the shortage or minimise the shortage impact.

The notification should be sent to the relevant authorities as early as possible even if information is limited. This can be supplemented at a later stage as further details become available as explained in section 7.

6. Who should be notified?

For all authorised medicinal products, shortage notifications should be sent to the impacted national competent authorities.

For centrally approved products, shortage notifications should be sent to EMA as well as the impacted national competent authorities.

MAHs should be aware of the appropriate authority that needs to receive shortage notifications (e.g. national regulatory body, national department of health). Details of the contact point are published on the website of the relevant competent authority. MAHs should be aware of the preferred process and format for reporting (e.g. email, pdf form, online data collection system).

7. What information should be included in notifications?

The information provided in the notification is used by the competent authority for triaging and assessing the situation. The information should therefore be as accurate and up-to-date as possible, while being comprehensive and concise at the same time.

HMA/EMA has developed a proposed template to be included within notifications (Annex 1) in cases where a reporting template is not available at national level. The MAH should endeavour to provide this information; however it is acknowledged that all of the below information may not be available at the time of notification or may change over time; outstanding or new information should be provided as soon as it becomes available or at a later point. Impact assessment details should be included when appropriate and as per national reporting practices/tools.

Individual Member States will determine the preferred method of notification (e.g. email, pdf form, online data collection system).

Annex 1: Proposed template for shortage notification

This form is not intended to notify competent authorities of the withdrawal of a marketing authorisation or a change in the marketing status of any particular product.

Template for shortage notification		
Product details	Product name*	
	Procedure Type (NAP, MRP/DCP, CP)	
	National Authorisation code/EMA Authorisation number*	
	Human medicine*	<input type="checkbox"/>
	Veterinary medicine*	<input type="checkbox"/>
	If veterinary, species authorised in MA	
	ATC code	
	Active substance(s)	
	Pharmaceutical form*	
	Strength*	
	Route(s) of administration	
	Pack size(s)	
Details on shortage	Date of the beginning of shortage(may be anticipated date)*	
	Expected end date of the shortage, if applicable*	
	Reason for shortage*	
	Impacted countries (if known)	
	Reference number of any Rapid Alert (quality/safety) related to the issue	
	Other authorities notified (e.g. other NCAs, EMA), including reference to Quality Defect report if relevant	
	Reference to related pending regulatory action, if relevant	
	Risk assessment of impact of shortage*	
	Proposed mitigation plan to deal with the shortage	
	Are any actions from NCA required? If yes, what actions?	
Details of notifying person	Company name and address (MAH, duly authorised representative or wholesale distributor, if applicable)	

	Name of the person completing the form and date	
	E-mail of contact person*	
	Telephone number contact person	
Impact assessment	<u>Potential</u> alternative medicinal products: <ul style="list-style-type: none"> ➤ Same medicine in different packaging size/strength/pharmaceutical form ➤ Other medicinal product with the same active substance: <ul style="list-style-type: none"> ○ the same strength ○ the same pharmaceutical form ○ the same route of administration ➤ Authorised and marketed products in the same class (therapeutic/pharmacological subgroup) with the same indications ➤ Authorised and marketed products in other class with the same approved indications 	
	Estimated size of population affected by the shortage of this product: <ul style="list-style-type: none"> ➤ Market share of the product* (hospital and ambulatory markets) ➤ Market sales volume (monthly/six monthly) and volume of prescriptions ➤ Proportion market sales affected by shortage ➤ Estimated stock in the current supply chain ➤ Stock that will be made available at the expected end date of the shortage and at the following supplies 	
	Considering: <ul style="list-style-type: none"> - Patient/animal safety - Will patients/animals have no access to a treatment? 	

* Minimum information to be provided to competent authority to proceed with the assessment of the case.

Annex 2: Extracts of relevant Union legislation

Regulation (EC) No 726/2004¹ (Human and Veterinary)

Article 13: "1. Without prejudice to Article 4(4) and (5) of Directive 2001/83/EC, a marketing authorisation which has been granted in accordance with this Regulation shall be valid throughout the Community. It shall confer the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State in accordance with Article 6 of Directive 2001/83/EC.

Authorised medicinal products for human use shall be entered in the Community Register of Medicinal Products and shall be given a number, which shall appear on the packaging.

2. Notification of marketing authorisation shall be published in the Official Journal of the European Union, quoting in particular the date of authorisation and the registration number in the Community Register, any International Non-proprietary Name (INN) of the active substance of the medicinal product, its pharmaceutical form, and any Anatomical Therapeutic Chemical Code (ATC).

3. The Agency shall immediately publish the assessment report on the medicinal product for human use drawn up by the Committee for Medicinal Products for Human Use and the reasons for its opinion in favour of granting authorisation, after deletion of any information of a commercially confidential nature.

The European Public Assessment Report (EPAR) shall include a summary written in a manner that is understandable to the public. The summary shall contain in particular a section relating to the conditions of use of the medicinal product.

4. After a marketing authorisation has been granted, the holder of the authorisation shall inform the Agency of the dates of actual marketing of the medicinal product for human use in the Member States, taking into account the various presentations authorised.

The marketing authorisation holder shall notify the Agency if the product ceases to be placed on the market of a Member State, either temporarily or permanently. Such notification shall, other than in exceptional circumstances, be made no less than two months before the interruption in the placing on the market of the product. The marketing authorisation holder shall inform the Agency of the reasons for such action in accordance with Article 14b.

Upon request by the Agency, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the Agency with all data relating to the volume of sales of the medicinal product at Community level, broken down by Member State, and any data in the holder's possession relating to the volume of prescriptions".

Article 38: "1. Without prejudice to Article 71 of Directive 2001/82/EC, a marketing authorisation which has been granted in accordance with this Regulation shall be valid throughout the Union . It shall confer the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State in accordance with Article 5 of Directive 2001/82/EC.

¹ Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency:

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

Authorised veterinary medicinal products shall be entered in the Union Register of Medicinal Products and shall be given a number which shall appear on the packaging.

2. Notification of marketing authorisation shall be published in the Official Journal of the European Union, quoting in particular the date of authorisation and the number in the Union Register, any International Non-proprietary Name (INN) of the active substance of the medicinal product, its pharmaceutical form, and any Anatomical Therapeutic Chemical Veterinary Code (ATC Vet Code).

3. The Agency shall immediately publish the assessment report on the veterinary medicinal product drawn up by the Committee for Medicinal Products for Veterinary Use and the reasons for its opinion in favour of granting authorisation, after deletion of any information of a commercially confidential nature.

The European Public Assessment Report (EPAR) shall include a summary written in a manner that is understandable to the public. The summary shall contain in particular a section relating to the conditions of use of the medicinal product.

4. After a marketing authorisation has been granted, the holder of the authorisation shall inform the Agency of the dates of actual placing on the market of the veterinary medicinal product in Member States, taking into account the various presentations authorised.

The holder shall also notify the Agency if the product ceases to be placed on the market, either temporarily or permanently. Such notification shall, other than in exceptional circumstances, be made no less than 2 months before the interruption in the placing of the product on the market.

Upon request by the Agency, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the Agency with all data relating to the volume of sales of the medicinal product at Union level, broken down by Member State, and any data in the holder's possession relating to the volume of prescriptions.

Cessation of placing of products on market (Human)

Directive 2001/83/EC²

Article 23a: "After a marketing authorisation has been granted, the holder of the authorisation shall inform the competent authority of the authorising Member State of the date of actual marketing of the medicinal product for human use in that Member State, taking into account the various presentations authorised.

If the product ceases to be placed on the market of a Member State, either temporarily or permanently, the marketing authorisation holder shall notify the competent authority of that Member State. Such notification shall, other than in exceptional circumstances, be made no less than two months before the interruption in the placing on the market of the product. The marketing authorisation holder shall inform the competent authority of the reasons for such action in accordance with Article 123(2).

Upon request by the competent authority, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the competent authority with all data relating to the

² Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use:
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

volume of sales of the medicinal product, and any data in his possession relating to the volume of prescriptions”.

Cessation of placing of products on market (Veterinary)

Directive 2001/82/EC³

Article 27a: “After a marketing authorisation has been granted, the holder of the authorisation shall inform the competent authority of the authorising Member State of the date of the actual placing on the market of the veterinary medicinal product in that Member State, taking into account the various presentations authorised.

The holder shall also notify the competent authority if the product ceases to be placed on the market of the Member State, either temporarily or permanently. Such notification shall, otherwise than in exceptional circumstances, be made no less than two months before the interruption in the placing on the market of the product.

Upon request by the competent authority, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the competent authority with all data relating to the volume of sales of the veterinary medicinal product, and any data in his possession relating to the volume of prescriptions”.

Regulation (EU) 2019/6⁴

Article 58.13: “The marketing authorisation holder shall without delay inform the competent authority which has granted the marketing authorisation or the Commission, as applicable, of any action which the holder intends to take in order to cease the marketing of a veterinary medicinal product prior to taking such action, together with the reasons for such action.”

Quality Defect (Human)

Commission Directive 2003/94/EC⁵

Article 13.1: “In the case of medicinal products, the manufacturer shall implement a system for recording and reviewing complaints together with an effective system for recalling, promptly and at any time, medicinal products in the distribution network. Any complaint concerning a defect shall be recorded and investigated by the manufacturer. The manufacturer shall inform the competent authority of any defect that could result in a recall or abnormal restriction on supply and, in so far as is possible, indicate the countries of destination.

Any recall shall be made in accordance with the requirements referred to in Article 123 of Directive 2001/83/EC”.

³ Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products:
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-5/dir_2001_82_cons2009/dir_2001_82_cons2009_en.pdf

⁴ Regulation (EU) 2019/6 of the European Parliament and of the council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC
<https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R0006&from=EN>

⁵ Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use:
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2003_94/dir_2003_94_en.pdf

Quality Defect (Veterinary)

Commission Directive 91/412/EC⁶

Article 13: "The manufacturer shall implement a system for recording and reviewing complaints together with an effective system for recalling promptly and at any time the veterinary medicinal products in the distribution network. Any complaint concerning a quality defect shall be recorded and investigation by the manufacturer. The competent authority shall be informed by the manufacturer of any quality defect that could result in a recall or abnormal restriction on the supply. In so far as possible, the countries of destination shall also be indicated. Any recall shall be made in accordance with the requirements referred to in Article 42 of Directive 8 11851 /EEC".

Continuity of Supply (Human)

Directive 2001/83/EC

Article 81: "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".

Continuity of Supply (Veterinary)

Regulation (EU) 2019/6

Article 58.2: "The marketing authorisation holder shall, within the limits of its responsibilities, ensure appropriate and continued supplies of its veterinary medicinal products."

Article 101.4: "Wholesale distributors shall, within the limits of their responsibility, ensure appropriate and continued supply of veterinary medicinal product to persons authorised to supply it in accordance with Article 103(1), so that the needs for animal health in the relevant Member State are covered."

⁶ Commission Directive of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products (91/412/EEC):

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-5/dir_1991_412/dir_1991_412_en.pdf