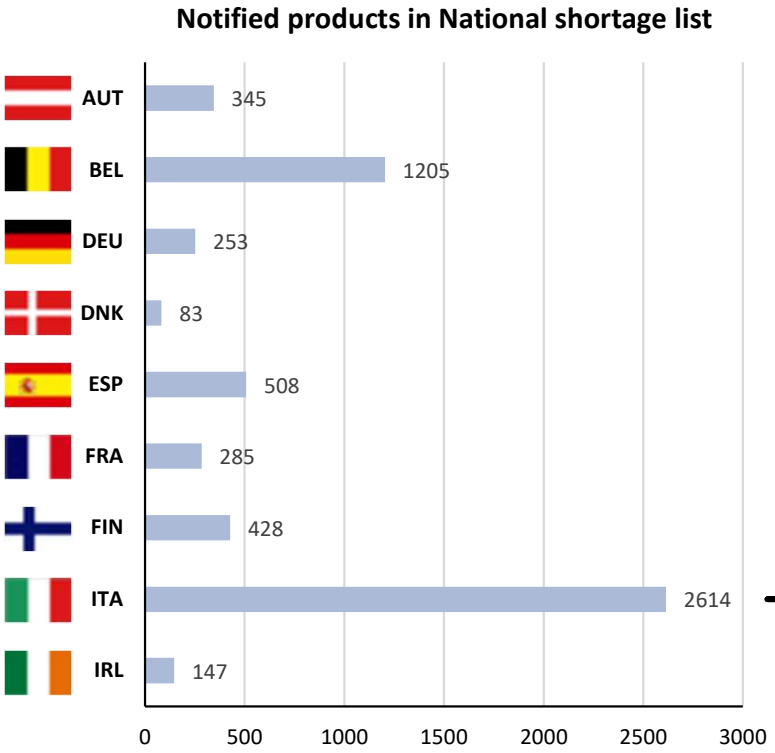
UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI
SCIENZE FARMACEUTICHE

The European resilience to medicines' shortages through the pandemic

Umberto M. Musazzi, PhD

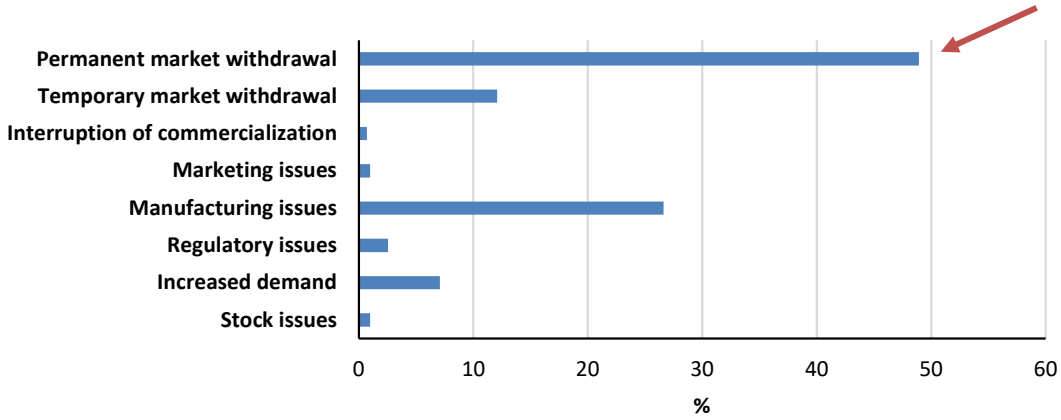
20th January 2022

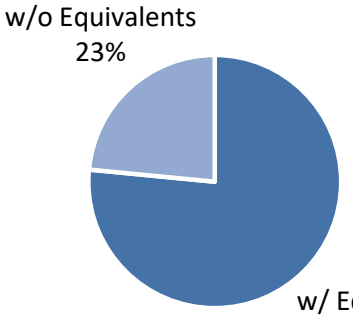
Medicine shortages in Europe

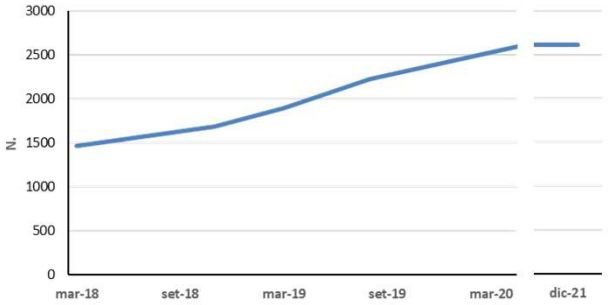


No. 116 ongoing shortages are reported in FDA database (https://www.accessdata.fda.gov/scripts/drugshortages/)

Focus on Italian situation (*)





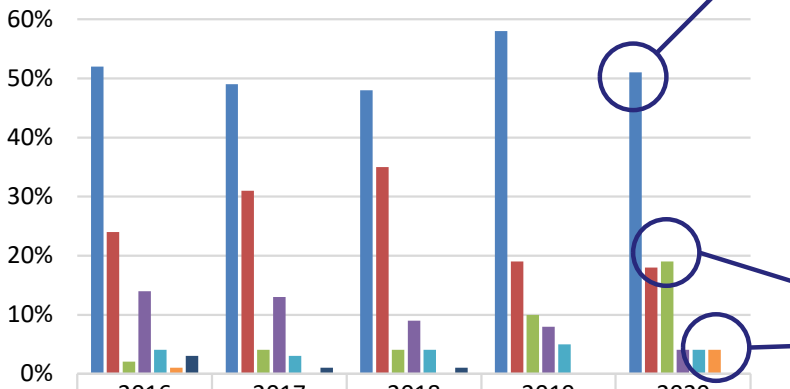


* Data extrapolated from the shortage list available on AIFA portal on 14/01/2022

Root causes

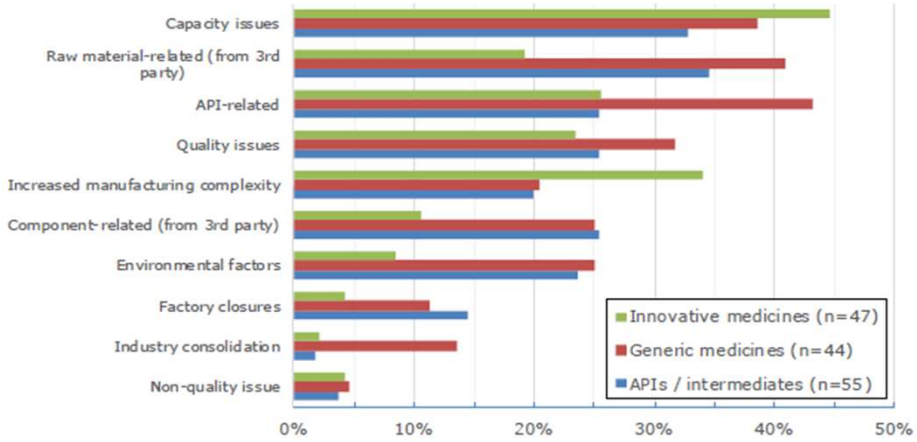
Future-proofing pharmaceutical legislation — study on medicine shortages
Final report

Time trends in reported root causes of shortages

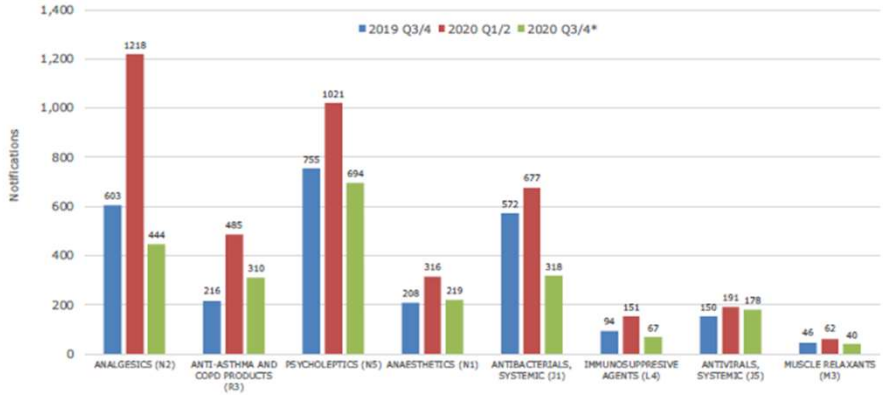


	2016	2017	2018	2019	2020
Quality & Manufacturing issues	52%	49%	48%	58%	51%
Commercial reasons	24%	31%	35%	19%	18%
Unexpected increased demand	2%	4%	4%	10%	19%
Distribution issues	14%	13%	9%	8%	4%
Regulatory issues	4%	3%	4%	5%	4%
Unpredicted major events or natural disasters	1%	0%	0%	0%	4%
Other issues	3%	1%	1%	0%	0%

Manufacturing-related factors that have affected the ability of manufacturers to ensure appropriate and continued supply

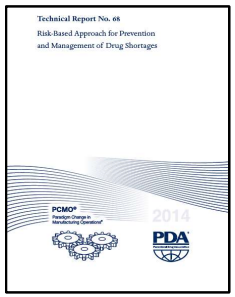


Notifications for categories containing products most used in COVID-19 treatment

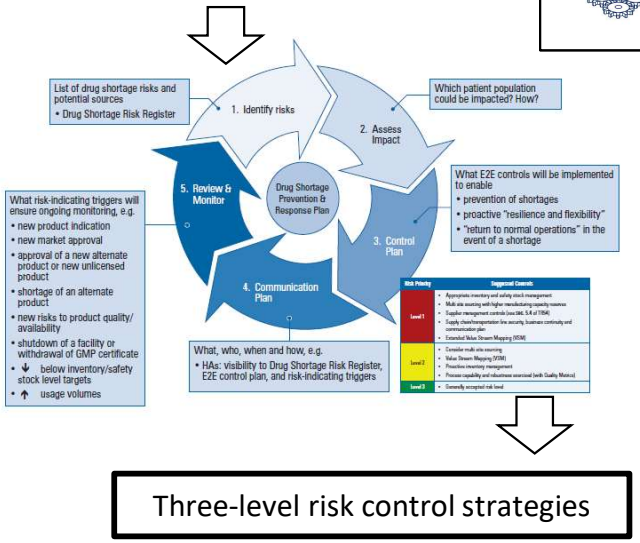


Preventing/mitigating strategies

Manufacturers



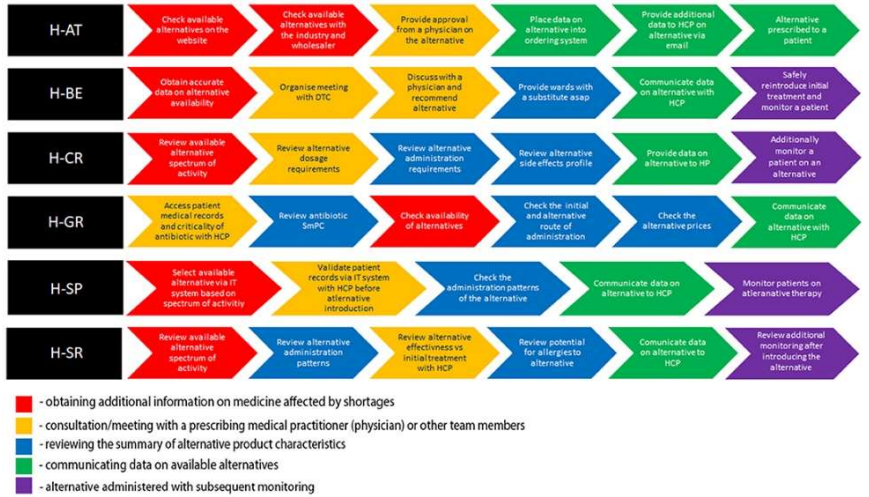
Shortage risk assessment



Three-level risk control strategies

Healthcare services

The heterogenicity in terms of risk assessment (e.g., FMEA, RCA, HFMEA, HACCP) and corrective strategies adopted in the European hospitals.



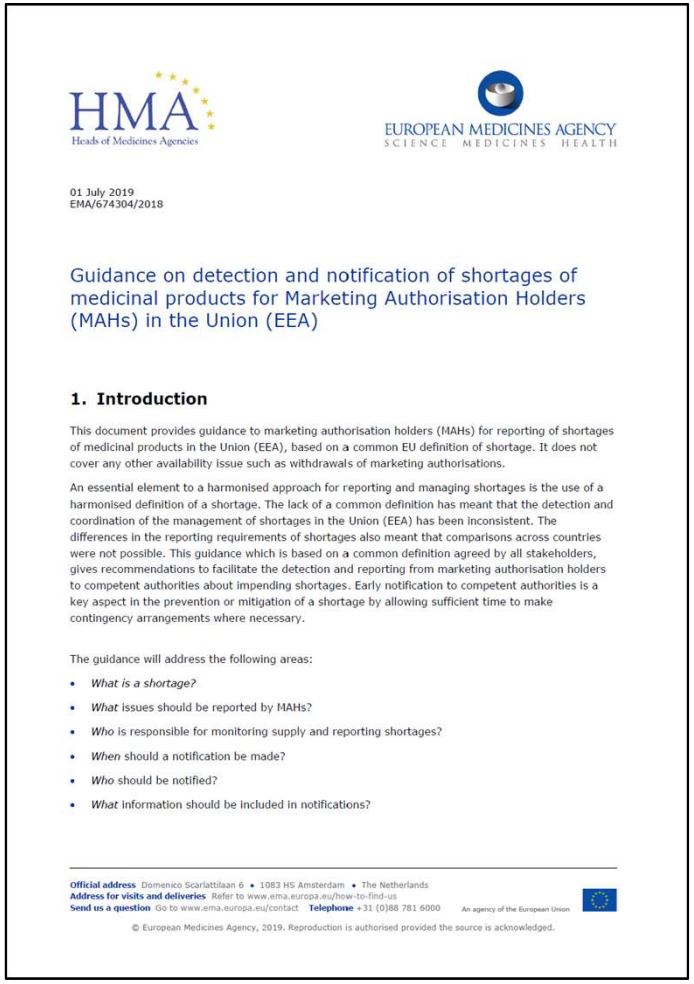
Color-coded flowchart highlighting similar patterns in sub-processes across health-care failure mode and effect analysis (HFMEA) study hospitals.

CA15105 - European Medicines Shortages Research Network - addressing supply problems to patients (Medicines Shortages)

Miljković et al. Front. Med., 2020, https://doi.org/10.3389/fmed.2020.00157
Miljković et al. Front. Med., 2020 https://doi.org/ 10.3389/fphar.2020.00357

Preventing/mitigating strategies

Regulatory authorities



HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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?

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The guidance provides information on:

- **SHORTAGE DEFINITION**
- 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

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

Regulatory authorities

Heterogenicity of shortage definition at national level

e.g., AIFA distinguishes:

Shortage (*carenza*)	A shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level (HMA/EMA guideline)
Unavailability (*indisponibilità*)	Delivery-related issues caused by distortions in distribution dynamics (e.g., parallel trade, distribution inefficiencies)
Missing hospital supply (*mancata fornitura ospedaliera*)	Medicines whose supplies are temporarily not guaranteed in the quantities and times intervals indicated in the supply contracts of healthcare structures/ regional purchasing center

https://www.aifa.gov.it/en/web/guest/farmaci-carenti

Preventing/mitigating strategies

To improve cooperation

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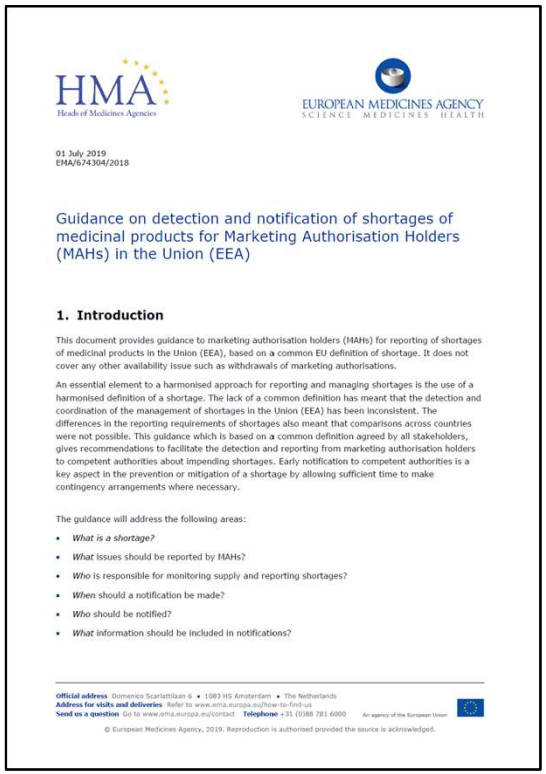
SINGLE NATIONAL POINTS OF CONTACT (SPOC) have been created to facilitate sharing of the information about nationwide medicine shortages and the coordination of emergency plans among the HMA members and the EMA.

COVID-19!! Each pharmaceutical company is appointing a single contact point (industry single point of contact or **i-SPOC**) who will report to EMA all ongoing or anticipated shortages of medicines used for treating COVID-19, irrespective of their authorisation route.

Preventing/mitigating strategies

To improve information sharing



HMA
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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

01 July 2019
EMA/674304/2018

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- *Who* should be notified?
- *What* information should be included in notifications?

The guidance provides:

- […]
- What information should be included in notifications

Template for shortage notification		
Product details	Product name*	
	Procedure Type (NAP, MRP/DCP, CP)	
	National Authorisation code/EMA Authorisation number*	
	Human medicine*	☐
	Veterinary medicine*	☐
	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	Potential alternative medicinal products: ➢ Same medicine in different packaging size/strength/pharmaceutical form ➢ Other medicinal product with the same active substance: ○ 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: ➢ 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: - Patient/animal safety - Will patients/animals have no access to a treatment?	

Mitigating strategies

To improve comunication to the public

HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4 July 2019
EMA/632473/2018

Good practice guidance for communication to the public on medicines' availability issues
Recommendations for EU national competent authorities and EMA to ensure adequate public information

The guidance aimed to enhance and align the European communication on a shortage to improve the awareness of healthcare professionals and patients and the cooperation among European stakeholders

Key recommendations for shortages		
Criteria for national competent authorities to make information publicly available	• shortages of medicines within their territory (nationwide issues rather than local issues). Ideally competent authorities should not apply selection criteria for publication and should communicate on all shortages occurring nationwide. In some instances, this communication may complement information issued centrally by EMA.	
Criteria for EMA to make information publicly available	• shortages of medicines (that are centrally or nationally authorised) where the shortage affects more than one member state and EMA's scientific committees have given recommendations to healthcare professionals (a DHPC).	
Format and tools	• **EU national competent authorities and EMA** should use a **systematic listing** (usually in the form of a catalogue, one for human medicines and one for veterinary medicines) to communicate on shortages. • For shortages with a high impact on patients or animals, consideration should be given to using high-profile communication tools (i.e. press release) in addition to systematic listing in the catalogue. • Regardless of the tools used, all shortages issues should be easily accessible on a webpage of the regulatory authority. • The content of the catalogue should be easily searchable. Non-machine readable data formats (such as PDFs) are not recommended and should be avoided as far as possible. Providing colour-coded or symbol-differentiated information for shortages could help to distinguish between different shortage situations (indicating impact and status of supply situation). • The use of electronic Product Information (ePI), once this is implemented across the EU, will offer opportunities to better communicate information on shortages in a timely and targeted manner.	
Information to be published in the catalogue	Details of medicine	• Trade name • Active ingredient (INN) • Pharmaceutical form and strength • MAH

Key recommendations for shortages		
		• For veterinary medicines the species
	Details on shortage	• Date of the beginning of the shortage (may be anticipated date) or availability issue • Expected end date of the shortage, if applicable • Reason for shortage and actions taken to mitigate shortage
	If applicable, advice for healthcare professionals patients, veterinarians or animal keepers	• Potential alternative medicinal products, if applicable, which may include imported medicines • Recommendations for change in clinical practice/ change in use of medicine/ use of a suitable alternative
	Updates to current status of shortage	• Updates should be issued to reflect resolution or any change in recommendations, if applicable
Timing of publication	• Publication should occur once the shortage has been confirmed by the marketing authorisation holder for the affected medicine and, if applicable, recommendations have been agreed. The exact timing may be determined at national level taking into account national requirements. However, early communication to the public is encouraged and important to allow for adequate planning and to ensure continuity of care. • Updates should be issued to reflect any relevant change in the situation including recommendations. For supply situations that have been resolved, this should be reflected as soon as the notification from the marketing authorisation holder has been received that the shortage is resolved. Once a shortage is declared as resolved, there may be a delay before supplies are fully re-established and it is recommended that a disclaimer is included to explain this in shortages communications. • A record of supply problems that have been resolved should be kept for a set period of time, i.e. at least 6 months.	
Audience	• Primarily healthcare professionals and patients, or veterinarians and animal owners. • Other regulators and industry (including wholesale distributors). To address this wide audience, the language used in any communication should be public friendly, concise and should use lay terms.	

Key recommendations for shortages	
Collaboration with stakeholders	• EU national competent authorities and EMA should consider involving relevant stakeholder groups (in particular patients', consumer and healthcare professional organisations) on availability issues, especially in those with higher potential impact on patient care. Wholesale distributors may also be involved for questions on sourcing of medicines. Involvement should aim at obtaining advice and feed-back on potential suitable alternatives and recommendations, if applicable, as well as feedback on whether key messages are well communicated and how to ensure adequate dissemination. • EU national competent authorities and EMA should consider sharing the final communication with marketing authorisation holders for information. • EU national competent authorities and EMA should explore ways to multiply their communication through relevant organisations' channels (patients, healthcare professionals, consumer organisations, animal owners, veterinarians), learned societies, professional/medical journals, media (press, TV), newsletters, and potentially electronic prescribing systems (enabling the electronic generation, transmission, and filling of a medical prescription). To increase visibility and knowledge about shortage catalogues, communication campaigns may be considered at national level.
Internal collaboration within the network	• For the assessment and communication of shortages, advice and consultation may be sought where needed from the Single Point of Contact (SPOC) network.[2] • Ideally, communication staff within EU national competent authorities or EMA should be involved in the drafting of relevant communication.

Key recommendations for other availability issues	
Criteria for national competent authorities to make information publicly available	• **revocations** or **suspensions** of marketing authorisations within their territory. • **relevant cessations of marketing authorisations** in their territory. For medicines, where the cessation of marketing authorisation is due to commercial reasons and other generic options remain on the market, the inclusion into the catalogue is optional.
Criteria for EMA to make information publicly available	• **revocation** or **suspension** of centrally and nationally authorised medicines.

Future-proofing pharmaceutical legislation — study on medicine shortages
Final report

Mitigating strategies

adopted by EU member states

Imports and distribution

- Exceptional imports of medicines not authorized in the MS
- Possibility to set quotas for the distribution of medicines
- Possibility to issue authorizations in absence of application
- Temporary derogatory authorization of medicines (e.g., packaging in another language; products close to expiry date; formal error in application)

Exports

- **Restrictions on parallel exports (and supporting measures)**
- Mandatory notification of exports

Additional obligations on MAHs and distributors

- **Obligation to supply directly to pharmacies and other end-distributors upon request**
- Obligation to import alternative medicines in case of shortage

Pharmacies, medical institutions, and end-users

- Minimum stock by pharmacies or healthcare units
- Daily reporting on stocks by pharmacies
- **Warning of supply issues by pharmacists (and patients)**

Information

- Advanced disclosures on stocks available and/or operations of MAHs and distributors
- Specific disclosure requirements in case of withdrawal

Reimbursement of medicines

- Limited reimbursement of medicines as a result of shortages

Other

- **Exceptional manufacturing activities by the State**
- Centralized purchasing and stockpiling at national level
- Prevention and/or mitigation plans required from MAHs
- Obligation to collaborate with the authorities
- Possibility for the NCA to declare shortages or risk thereof independently of notifications
- **Ad-hoc agreements with MAHs**
- **Surveillance program and inspections**

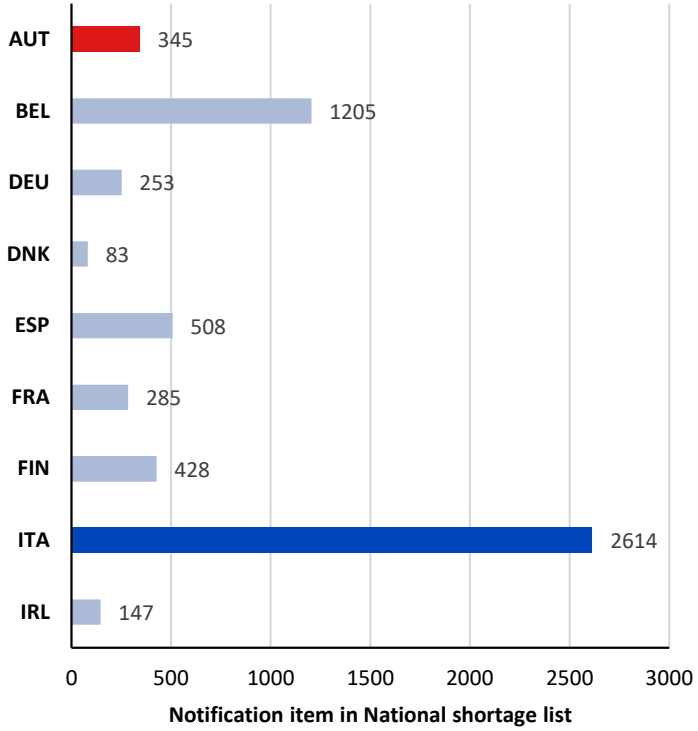
Strategies adopted in Italy

…to improve the communication and cooperation among the European Countries and pharmaceutical stakeholders.

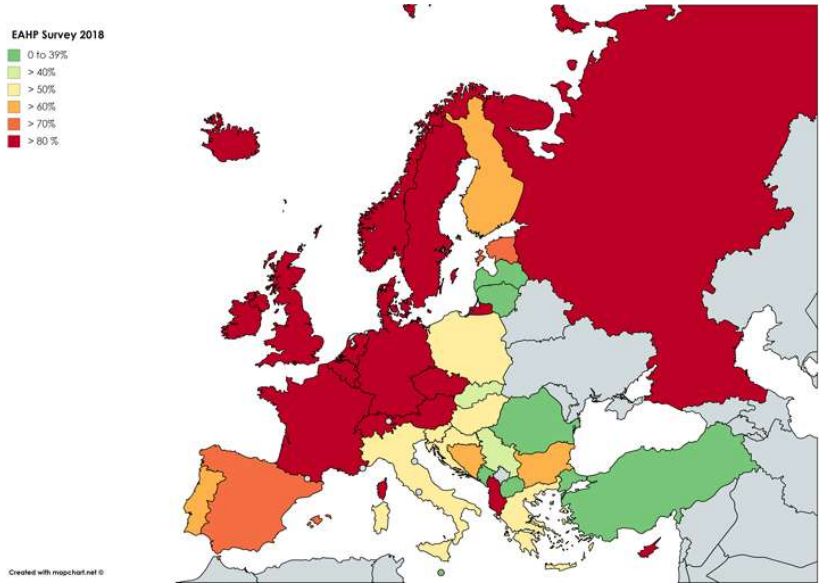
What are the problems still on the ground?

- Bias between numbers and how they are perceived;
- Harmonized metrics and impact assessment methodologies.

Numbers and how they are perceived



The map below shows the percentage of pharmacists in each country reporting a shortage occurring on a weekly or even daily basis (based on EAHP report, 2018).



	AUT	BEL	DEU	DNK	ESP	FRA	FIN	ITA	IRL
Generic medicine substitution is legally allowed?	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Medicines for Europe - Market Review – European Generic Medicine Markets 2020

Future-proofing pharmaceutical legislation — study on medicine shortages
Final report

"A potential solution to mitigate the impact of shortages, is to enable pharmacists to independently decide on appropriate substitutions for a medicine in shortage and dispense this directly to the patient without mandating consultation with a prescriber."

Shortage

MAH notification

MAH notification

EMA/National Competent Authorities

Communication to the public

EMA/national shortage list; Communication to the public and healthcare professionals

Information sharing using SPOC/i-SPOC system

Adoption of corrective strategies

Effective?

yes

no

Emergency is over

FDA

Adoption of prevention strategies

Effective?

yes

no

Emergency is over

FDA shortage list; Communication to the public and healthcare professionals

New!!

Press release

20-01-2022 - 09:08
20220114IPR21015

European Parliament

Health Union: a stronger role for the European Medicines Agency

- Better crisis preparedness and management for medicinal products and medical devices
- New EU platform to monitor and report medicine shortages
- Increased transparency on shortages, clinical trials and marketing authorisations

UNIVERSI
FACOLTÀ

Publicly available guidelines

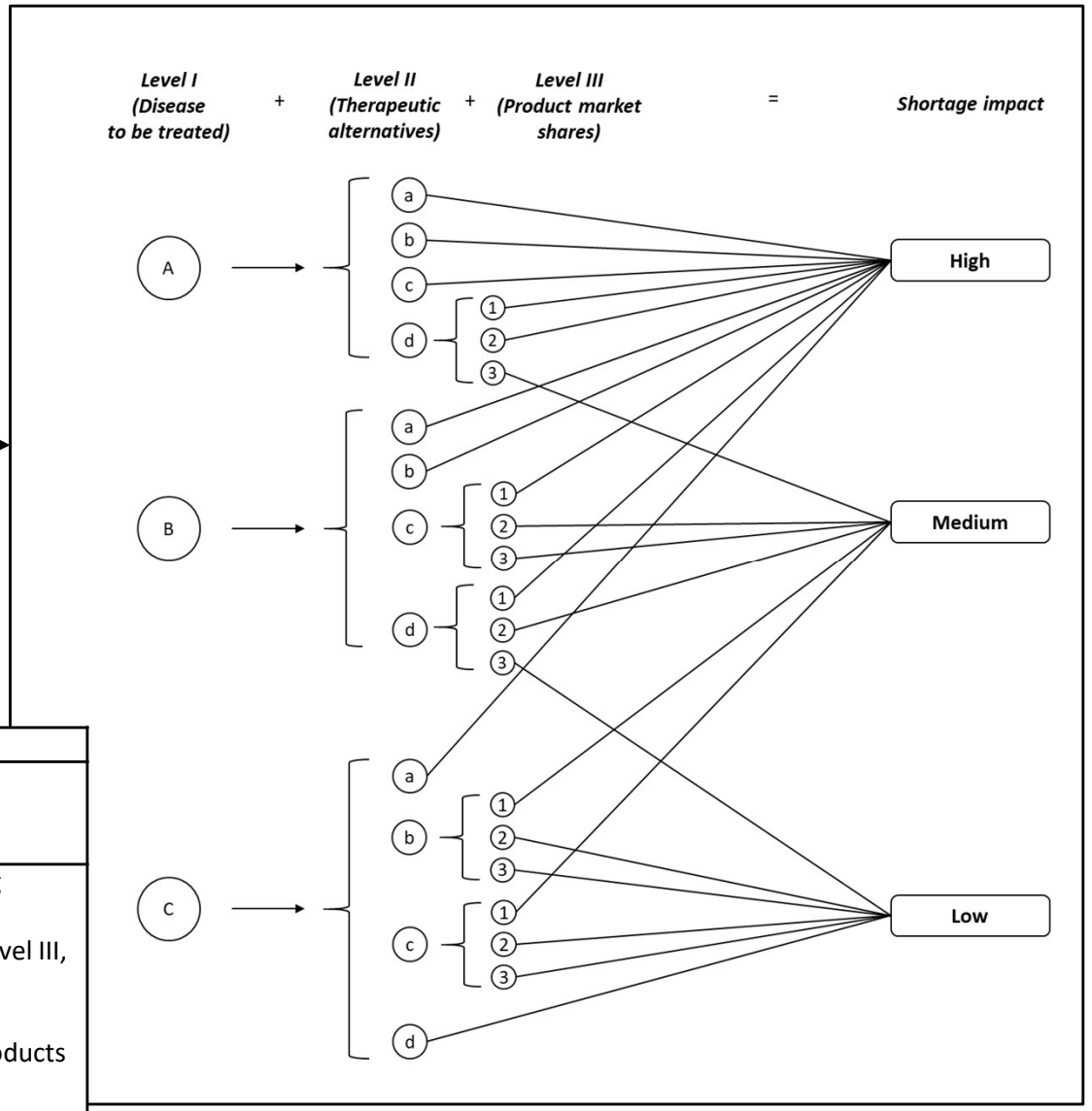
No publicly available guidelines

Metrics and risk assessment of shortage impact

Notification process

EMA/National competent Authorities

Algorithm to define the shortage impact on patient health



Level	Score
I	A. Life-supporting, life-sustaining or rare diseases; B. Serious or debilitating diseases (acute or chronic); C. Other diseases
II	a. Not more than two medicinal products containing drug substances in the same ATC level III or IV; b. More than two medicinal products for the same ATC level III, but not for the same ATC level IV; c. More than two medicinal products containing drug substances in the same ATC level IV, but no generic products are available for the same ATC level V; d. More than two generic products for the same ATC level V.
III	1. Market shares higher than 50% (annual product volumes); 2. Market shares between 25-50% (annual product volumes); 3. Market shares lower than 25% (annual product volumes).

Musazzi et al. Int J Pharm (2020), doi: 10.1016/j.ijpharm.2020.119171

Metrics and risk assessment of shortage impact

Notification process

EMA/National competent Authorities

Algorithm to define the shortage impact on patient health

(Regulatory Authorities and other subjects involved in national pharmaceutical distribution chains and healthcare systems)

Based on shortage impact assessment, adoption of the most appropriate preventive/mitigation strategies…

…to improve resilience of manufacturing and distribution chains	e.g., exceptional manufacturing activities by Member States for medicines with a high shortage impact.
…to improve economic sustainability	e.g., economic incentives to sustain manufacturers of less profitable medicines with a high shortage impact
…to control export/import	e.g., block of exportation of medicines with a high/medium shortage impact
…to communicate to the public	e.g., communication channels selected based on drug shortage impact

Musazzi et al. Int J Pharm (2020), doi: 10.1016/j.ijpharm.2020.119171

Thank you
for your kind attention!