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Health Products Regulatory Authority

Medicine Shortages: An update on the multi-stakeholder framework

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Medicine Shortages & Borderline Classification, Compliance, HPRA

9th October 2024

What is a medicine shortage?

A shortage is defined as occurring when:

The supply of a medicinal product is inadequate to meet the needs of patients

The World Health Organisation recognises medicine shortages as a global problem. They represent an increased focus for governments given their potential public health impact

What is a medicine shortage?

- All authorised medicines are included within the scope of the definition (i.e. prescription and non-prescription medicines)
- There is a supply and demand perspective; where there is no demand for a medicine to treat patients, a shortage of this product does not have significance for patients
- The definition is applied at an individual product level; this means that a specific medicine could be defined as being in short supply even if there are equivalent alternatives available
- Discontinuations/withdrawals are not considered shortages

What is not considered a medicine shortage?

- Where a medicine is not yet authorised or which is authorised and not marketed in Ireland for commercial reasons
- A delay in supply of a medicine to a pharmacy due to logistic reasons or an error in delivery
- Where normal supply to a wholesale distributor has been delayed, but there is sufficient stock at wholesale level that normal supply to patients will not be impacted
- Where only one wholesaler is not in a situation to supply the particular medicine and others can supply the medicine

How do medicine shortages occur? Supply chain….

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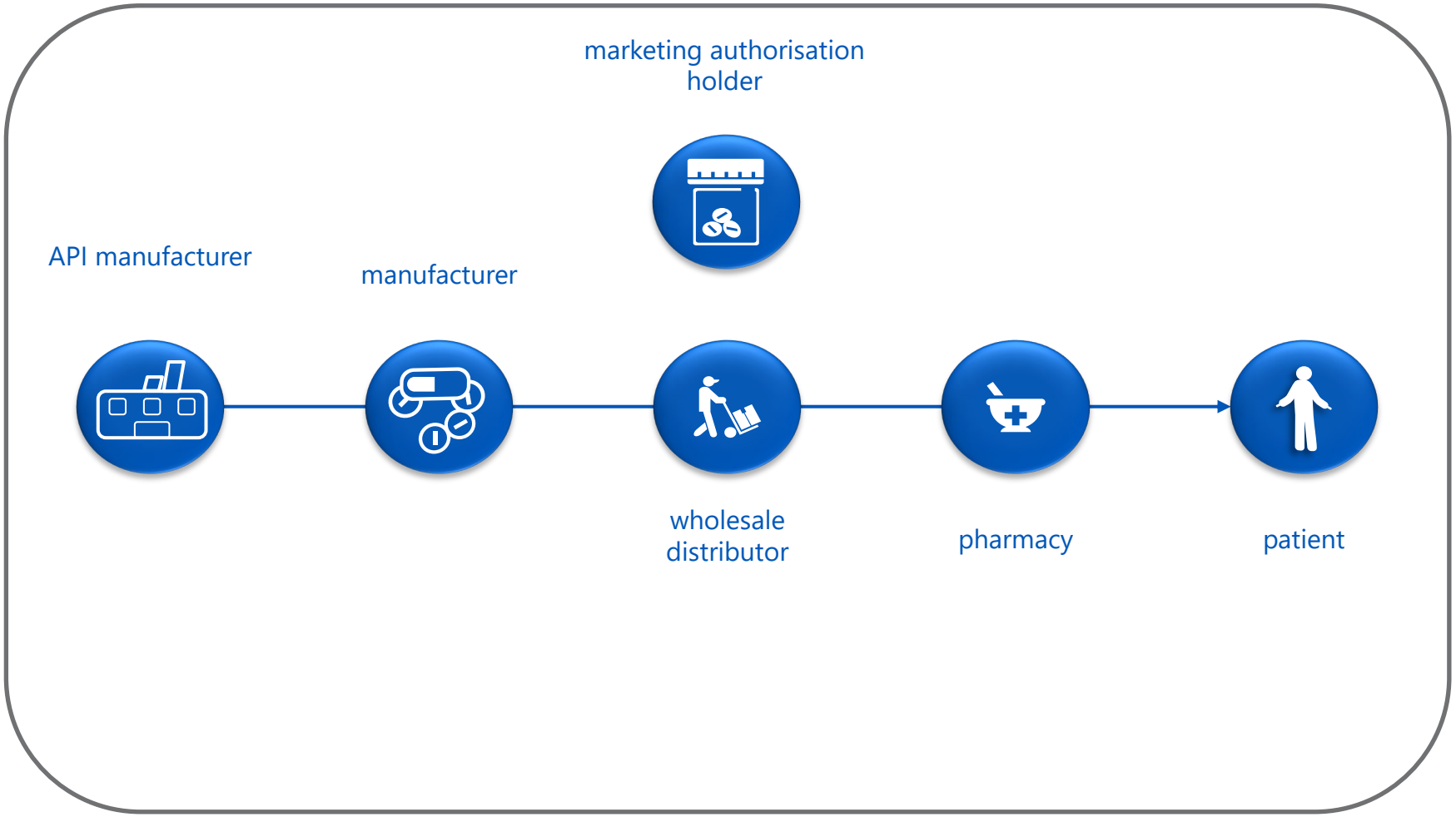
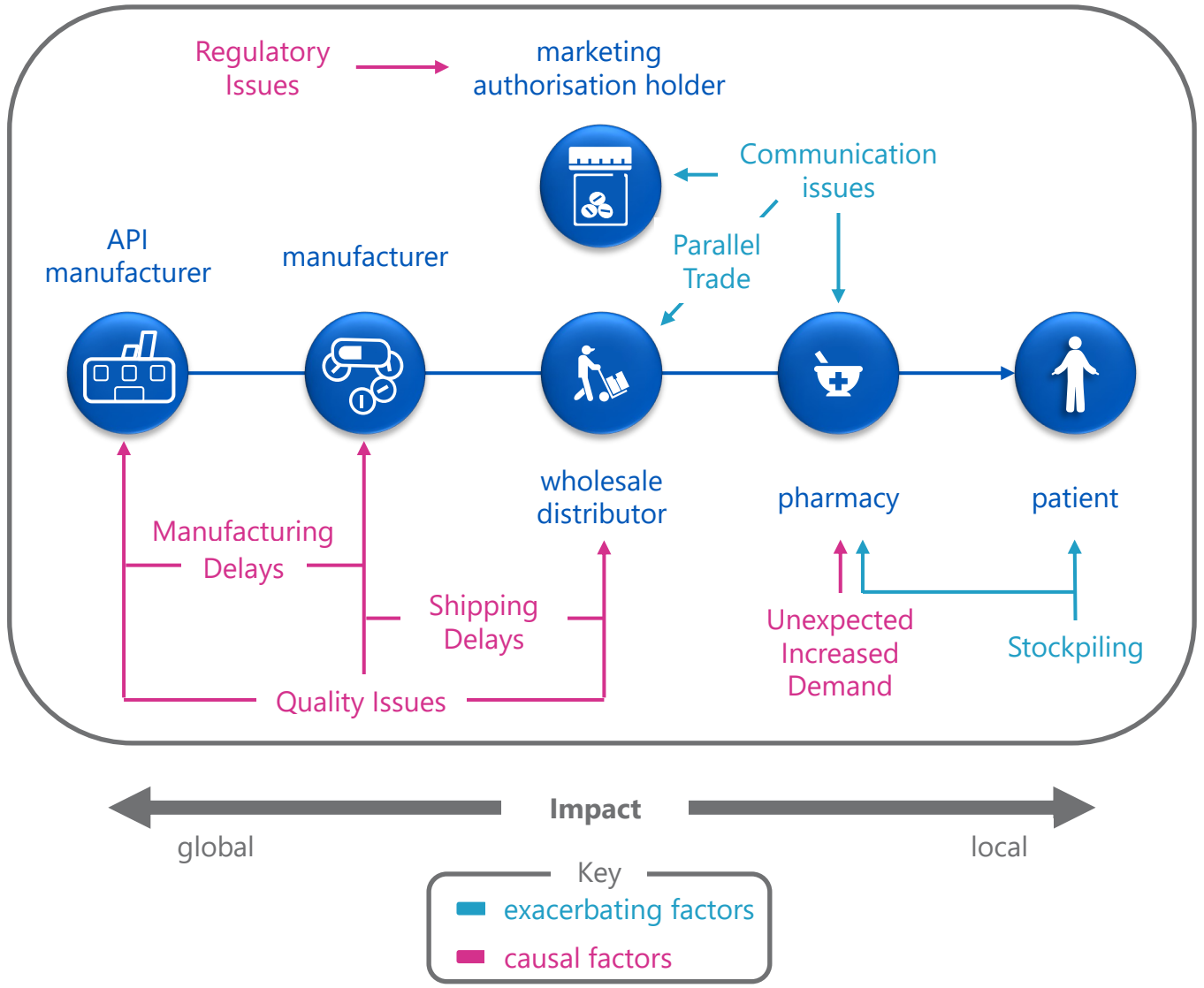


Why do medicine shortages occur?

Each shortage represents an individual set of circumstances. From industry information received by the HPRA, we know that:

- Over 60% of shortages relate to delays or breakdowns during manufacturing or a product quality issue
- Manufacturing can also be delayed when an active substance or other ingredient is in short supply. Shortages in packaging materials etc can also lead to delays
- Unexpected increased demand can cause or exacerbate certain shortages. This could be due to an increase in prescribing of a particular medicine. Greater than anticipated levels of seasonal illness can also result in shortages of medicines needed to treat those illnesses

Supply chain



Supply chain

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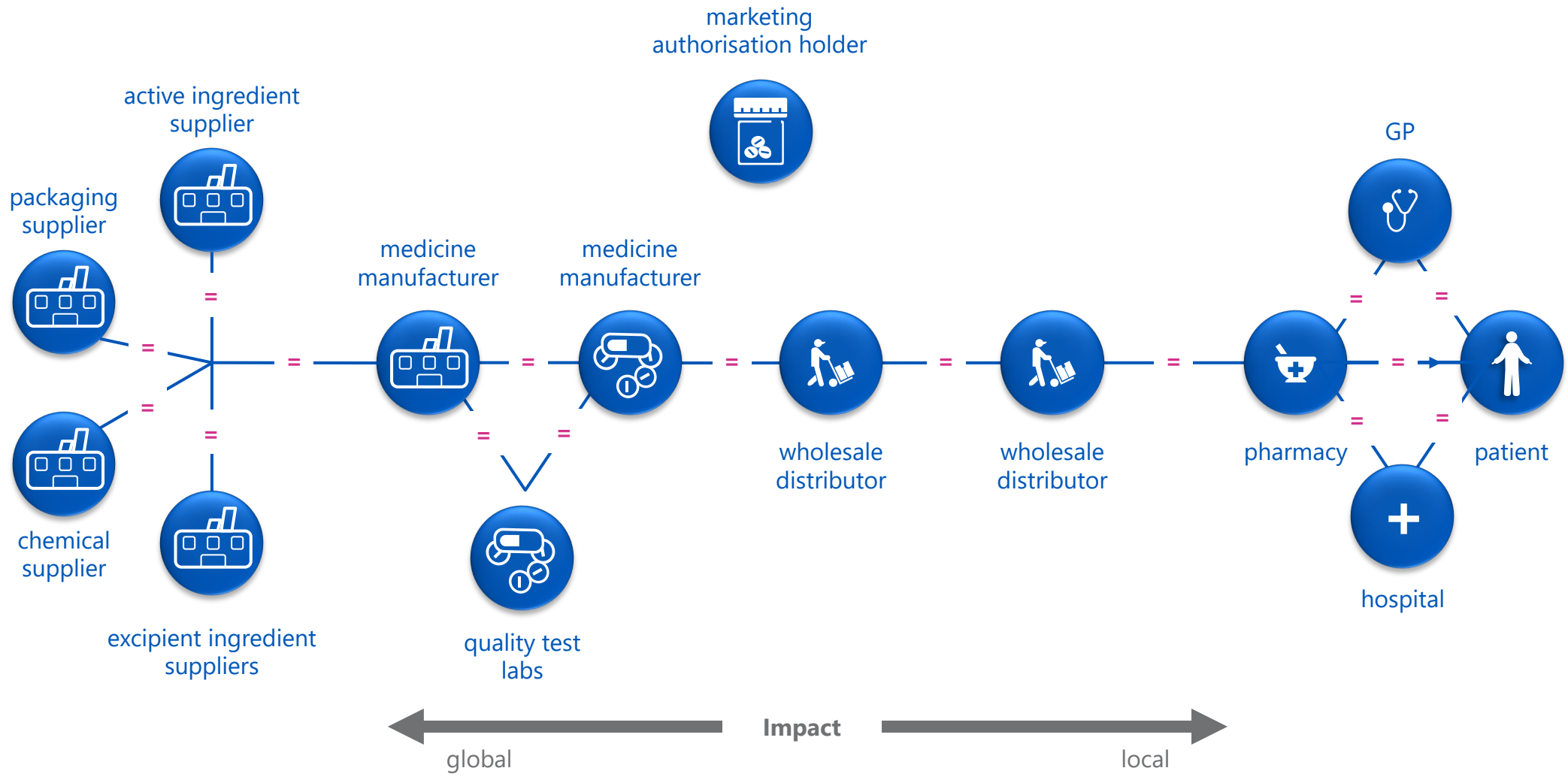

Supply chain

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manufacturing delays

- CMO-related
- equipment breakdown
- site transfer
- packaging
- cyber attack

quality issues

- QDR-related
- sterility issues
- QC test failure

unexpected increased demand

- shortage of competitor product
- uptake of different strength
- recall
- pandemic/outbreak
- *(often link to other reasons)*

regulatory issues

- delay in submission of variation
- no approved API
- delay in CD licence application

shipping delay

- local delay confirming order
- system error
- industrial action
- delay supply from manufacturer to wholesale

How are medicine shortages handled via the framework?

- The HPRA oversees a multi-stakeholder framework intended to address the issue of human medicine shortages in Ireland
- The aim of the framework is to:

1. Help avoid potential shortages from occurring in the first place
2. Reduce the impact on patients when shortages do occur

Multi-stakeholder framework

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Responsibilities of Marketing Authorisation Holders MAH

- MAHs are legally obliged, within the limits of their responsibilities, to ensure appropriate and continued supplies to meet the needs of patients in the State
- Oversight of the supply of their medicines nationally and globally allows for alignment of supply & demand
- Assess impact of a shortage on patients, notify the HPRA and prepare an appropriate response

Responsibilities of Stakeholders

marketing authorisation holders

- continued supply of medicines
- supply chain oversight
- impact assessment
- response

manufacturers

- continued supply of medicines
- capacity to increase production
- support impact assessment

HSE

- policy and operational aspects
- pricing agreements
- clinical guidance

HPRA

- co-ordination
- regulatory action
- communication

Department of Health

- overarching policy and direction
- pricing agreements
- legislation

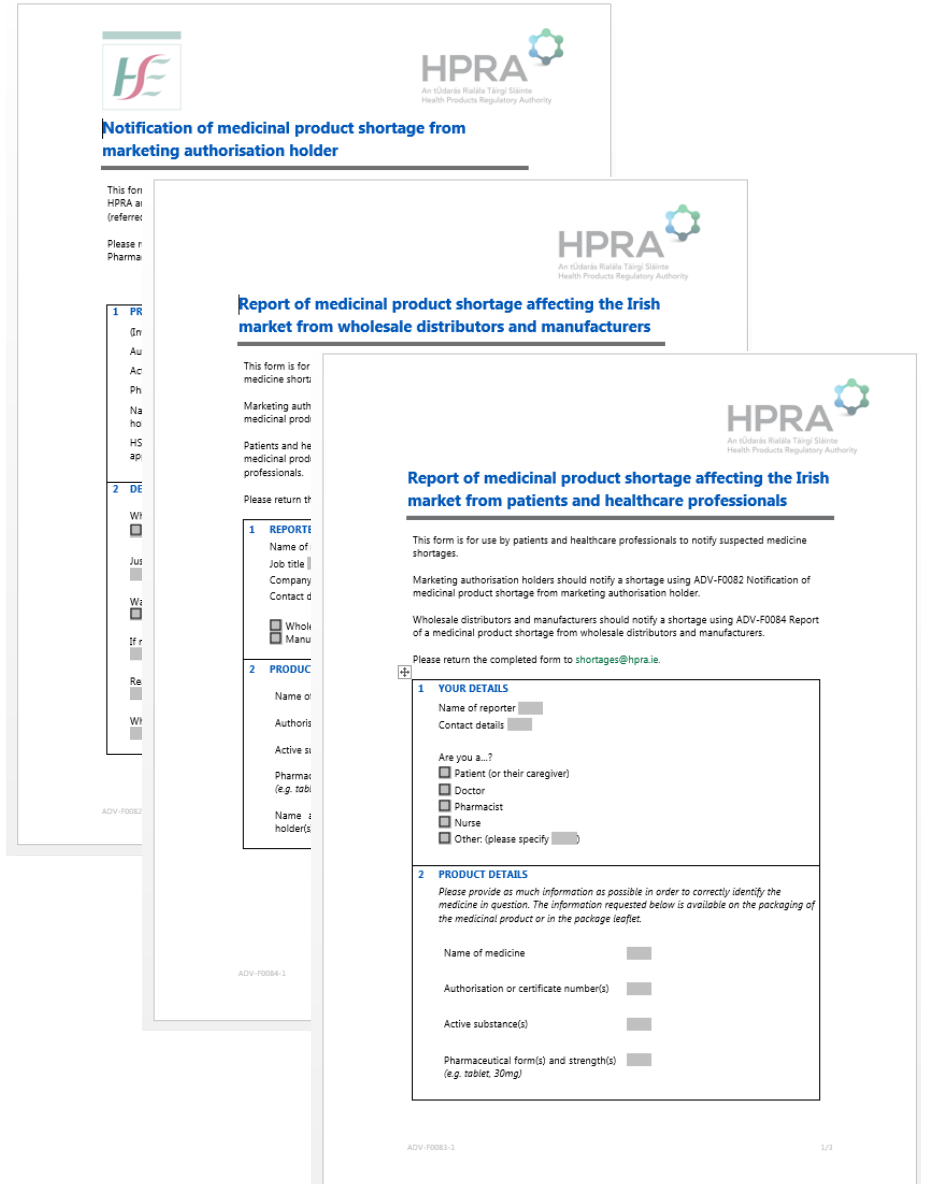
patient representative groups

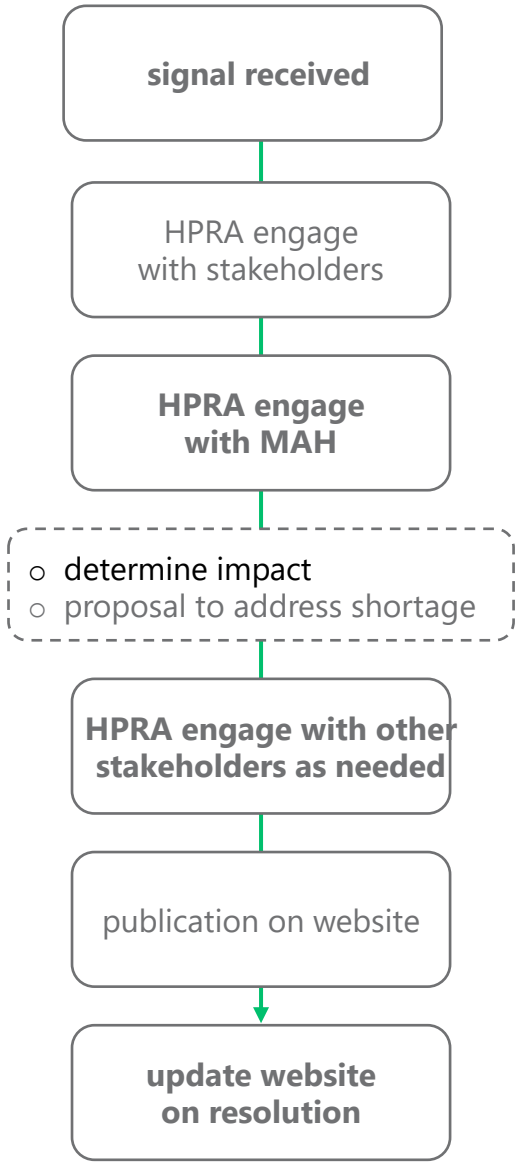
- supporting patients
- information provision

healthcare professionals

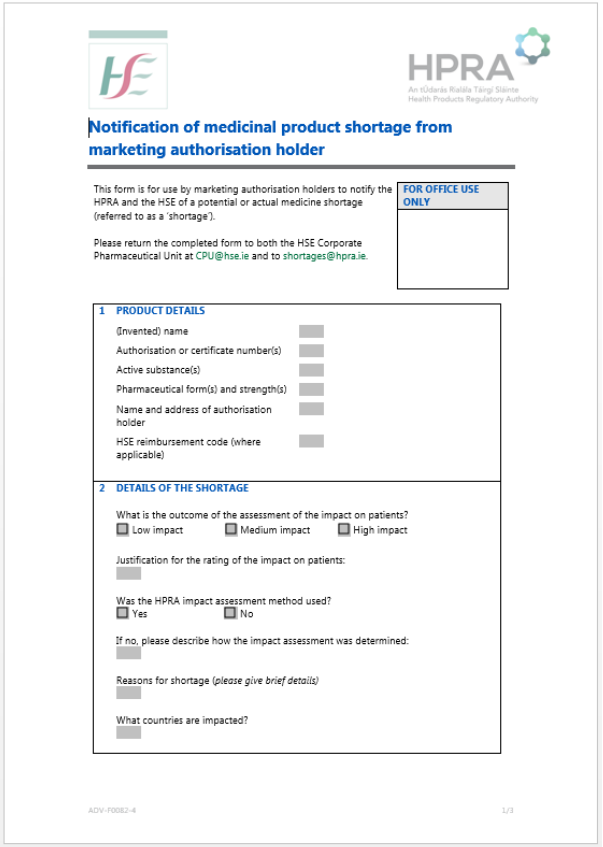
- identify alternatives
- good citizenship

HPRA Coordination role





HPRA Coordination role



Notification of medicinal product shortage from marketing authorisation holder

This form is for use by marketing authorisation holders to notify the HPRA and the HSE of a potential or actual medicine shortage (referred to as a 'shortage').

Please return the completed form to both the HSE Corporate Pharmaceutical Unit at CPU@hse.ie and to shortages@hpra.ie.

FOR OFFICE USE ONLY

1 PRODUCT DETAILS

(Invented) name

Authorisation or certificate number(s)

Active substance(s)

Pharmaceutical form(s) and strength(s)

Name and address of authorisation holder

HSE reimbursement code (where applicable)

2 DETAILS OF THE SHORTAGE

What is the outcome of the assessment of the impact on patients?
☐ Low impact ☐ Medium impact ☐ High impact

Justification for the rating of the impact on patients:

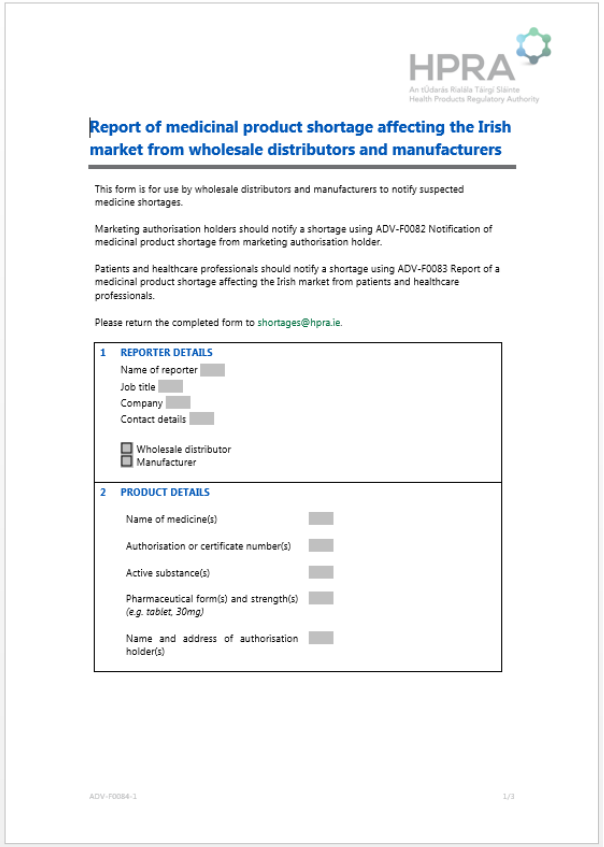
Was the HPRA impact assessment method used?
☐ Yes ☐ No

If no, please describe how the impact assessment was determined:

Reasons for shortage *(please give brief details)*

What countries are impacted?

ADV-F0082-4 1/3



Report of medicinal product shortage affecting the Irish market from wholesale distributors and manufacturers

This form is for use by wholesale distributors and manufacturers to notify suspected medicine shortages.

Marketing authorisation holders should notify a shortage using ADV-F0082 Notification of medicinal product shortage from marketing authorisation holder.

Patients and healthcare professionals should notify a shortage using ADV-F0083 Report of a medicinal product shortage affecting the Irish market from patients and healthcare professionals.

Please return the completed form to shortages@hpra.ie.

1 REPORTER DETAILS

Name of reporter

Job title

Company

Contact details

☐ Wholesale distributor
☐ Manufacturer

2 PRODUCT DETAILS

Name of medicine(s)

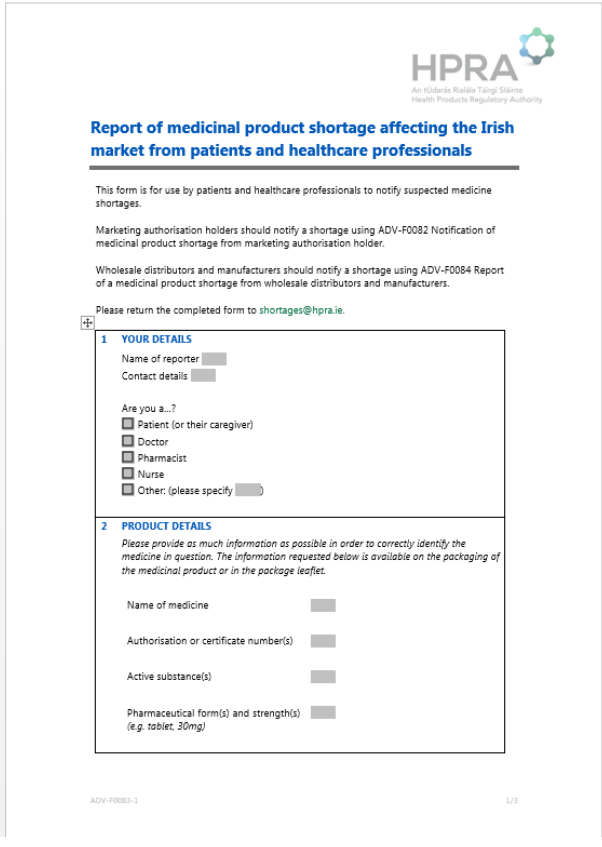
Authorisation or certificate number(s)

Active substance(s)

Pharmaceutical form(s) and strength(s) *(e.g. tablet, 30mg)*

Name and address of authorisation holder(s)

ADV-F0084-1 1/3



Report of medicinal product shortage affecting the Irish market from patients and healthcare professionals

This form is for use by patients and healthcare professionals to notify suspected medicine shortages.

Marketing authorisation holders should notify a shortage using ADV-F0082 Notification of medicinal product shortage from marketing authorisation holder.

Wholesale distributors and manufacturers should notify a shortage using ADV-F0084 Report of a medicinal product shortage from wholesale distributors and manufacturers.

Please return the completed form to shortages@hpra.ie.

1 YOUR DETAILS

Name of reporter

Contact details

Are you a...?
☐ Patient (or their caregiver)
☐ Doctor
☐ Pharmacist
☐ Nurse
☐ Other: (please specify)

2 PRODUCT DETAILS

Please provide as much information as possible in order to correctly identify the medicine in question. The information requested below is available on the packaging of the medicinal product or in the package leaflet.

Name of medicine

Authorisation or certificate number(s)

Active substance(s)

Pharmaceutical form(s) and strength(s) *(e.g. tablet, 30mg)*

ADV-F0083-1 1/3

HCP Reports: shortages@hpra.ie

MAH Notifications: shortages@hpra.ie and cpu@hse.ie

When should medicine shortages be reported/notified?

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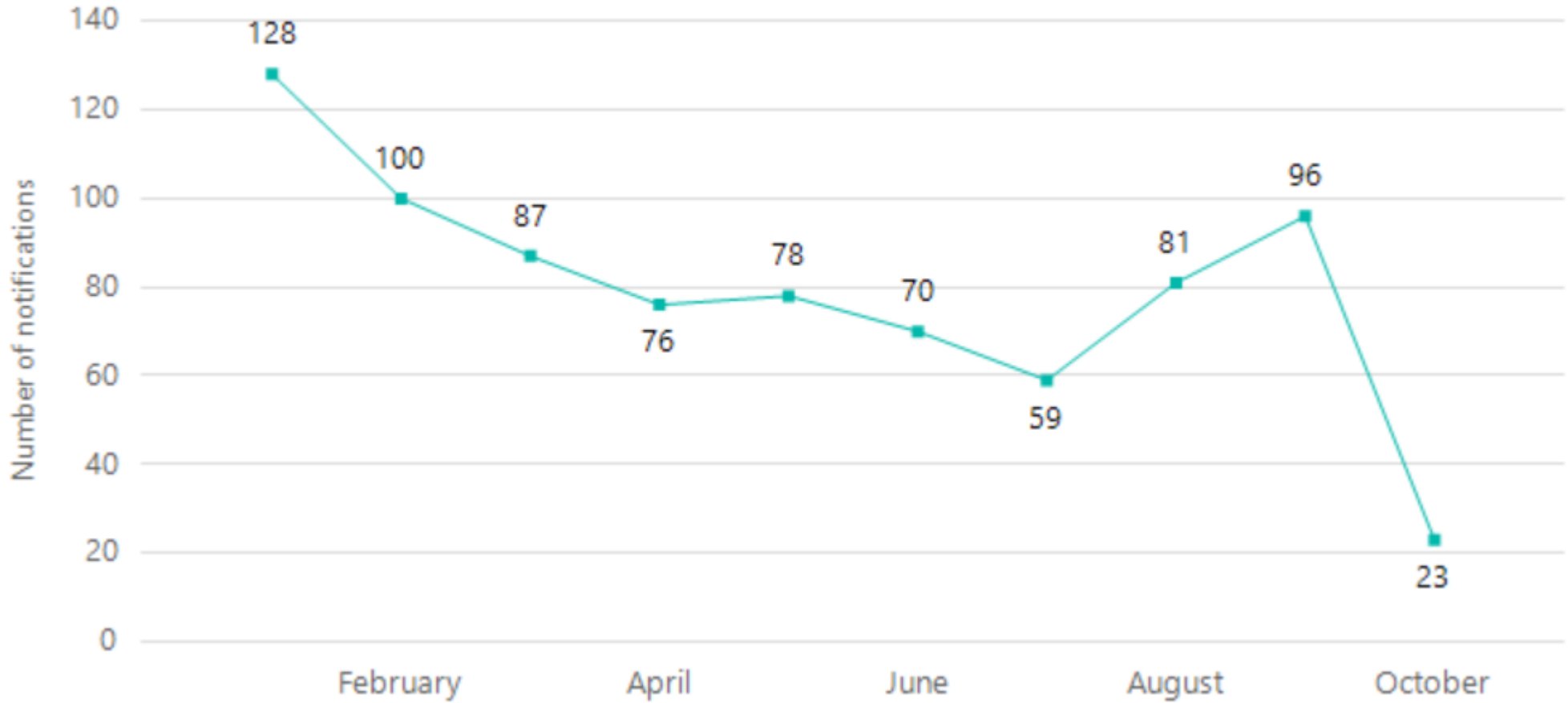
	Low impact shortages	Medium and high impact shortage
Timeframe	• Not less than one month in advance of a shortage	• As soon as possible (*including potential shortage*)
Information required from MAH	• Notification form	• Notification form • Proposal for handling shortage (including supporting material for patients or healthcare professionals, if appropriate)
Information required from other stakeholders	• Details of the product • Circumstances of potential shortage • Communication with stakeholders relating to the issue (*e.g. contacting more than one supplier, contacting the MAH*)	• Details of the product • Circumstances of potential shortage • Communication with stakeholders relating to the issue (*e.g. contacting more than one supplier, contacting the MAH*)

Average number of notifications from 2024 : January to 2024 : October **80**



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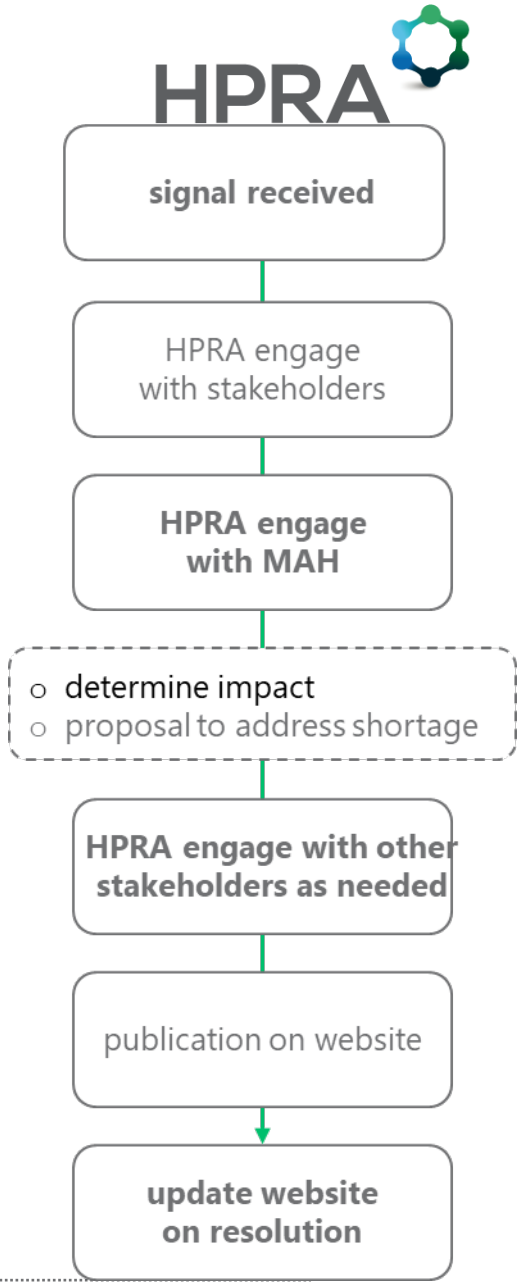
Shortage notification

- Early notification of a potential or actual medicine shortage is critical in helping to prevent or mitigate a shortage
- The assessment of and response to medicine shortages may involve the co-ordination of advice and activities by a range of stakeholders and experts
- Impact assessments, shortage notifications and updates should be reliable, timely, consistent and comprehensive

Impact Assessment

Combines two main considerations:

1. The availability of therapeutic alternatives and
2. The potential impact on patients



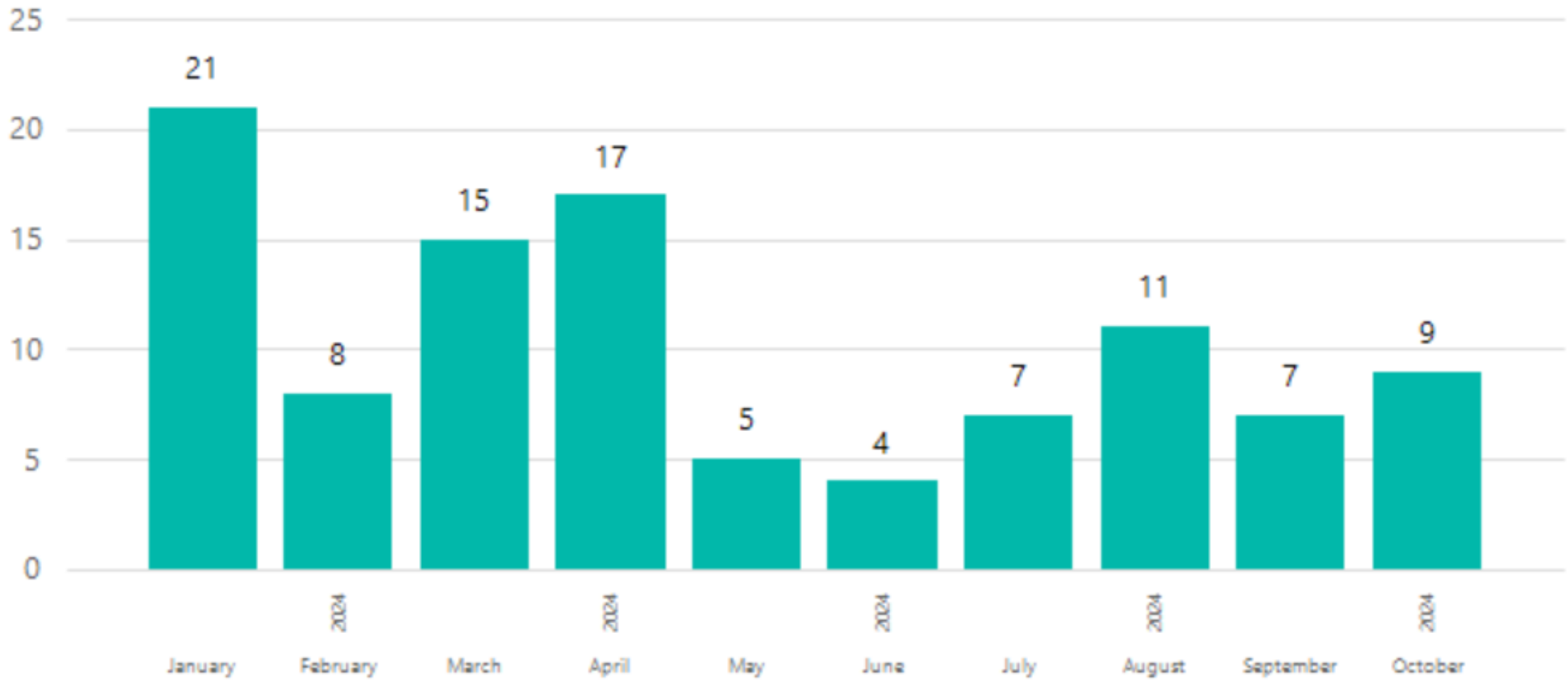
Therapeutic alternative		Description	Examples
Determined by taking into account: • Types of therapeutic alternatives that exist • Approved indications of the alternative medicine • Likelihood of alternative being available • Feasibility of the alternative therapy substitution in the context of the patient population and care setting. • Patient safety	Exact	• Same active ingredient, strength and pharmaceutical form	• Available generic
	Similar	• Same active ingredient but different strength	• Different strength tablet
	Appropriate	• Different active but same pharmacological class • Same active but different formulation that may need consideration of care setting	• Proton pump inhibitors • Statins • Antibiotics[1] • Oral for intravenous substitution
	Comparable	• Different active but comparable pharmacological class or mode of action that manages symptoms	• Management of chronic diseases (e.g. diabetes) • ACE inhibitor and angiotensin receptor antagonist
	None	• Unique pharmacology, no alternative treatment option exists	• Certain vaccines

Impact on patient		Example
Determined by taking into account: • The unique needs of the patient population • Consequence of a shortage on the likelihood of the condition progressing if left untreated, from a less serious to more serious condition	Mild	• Simple dermatological conditions
	Moderate	• Vulnerable patient populations where some dose forms may not be appropriate
	Severe	• Oncology patients, mid-cycle of a regimen • Certain antibiotics[1]

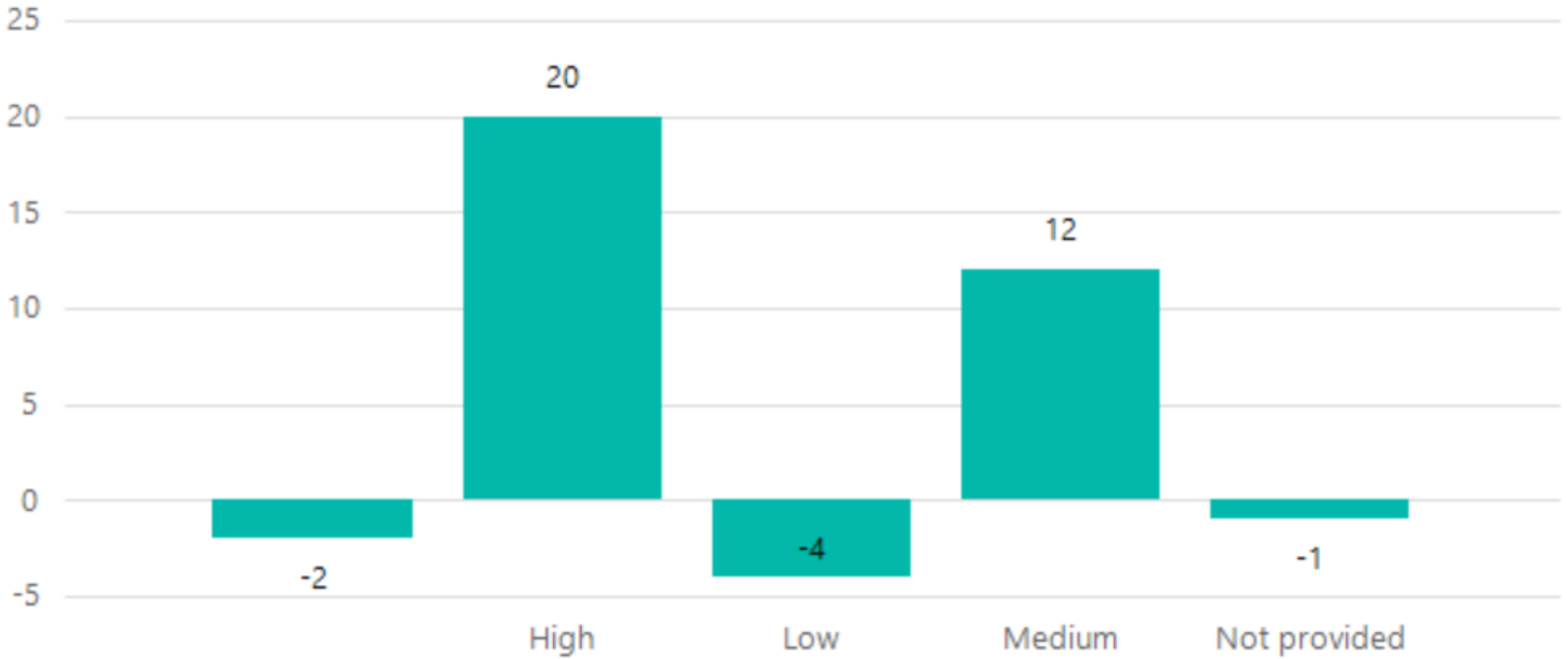
Impact Assessment

	Therapeutic alternative				
Impact on patient	**Exact**	**Similar**	**Appropriate**	**Comparable**	**None**
Mild	Low	Low	Medium	Medium	High
Moderate	Low	Medium	Medium	High	High
Severe	Low	Medium	High	High	High

Average timing of notification : 11

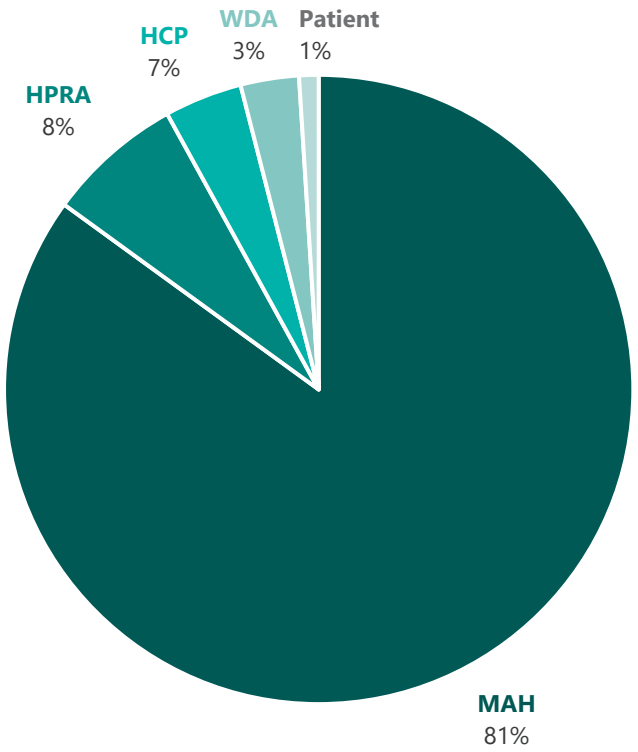


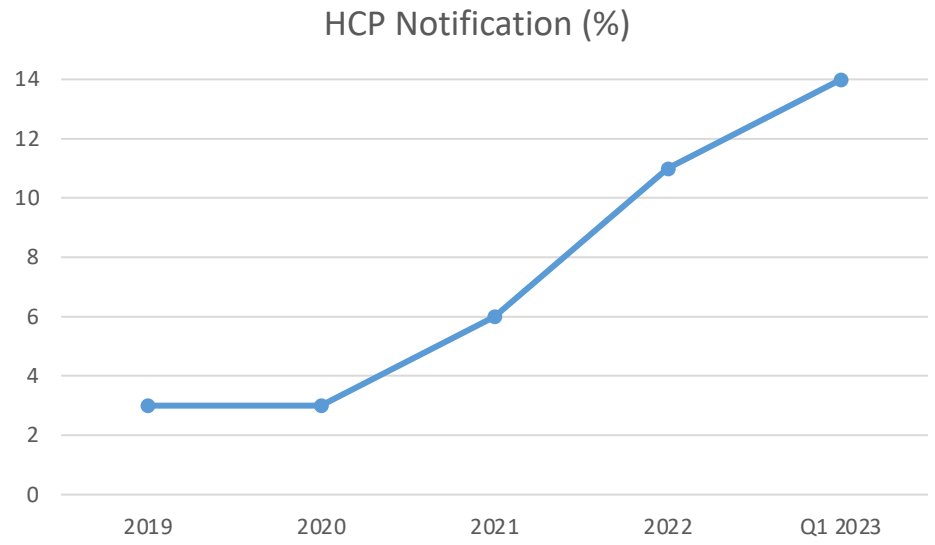
Average timing of notification by impact



Shortages Two Year review data

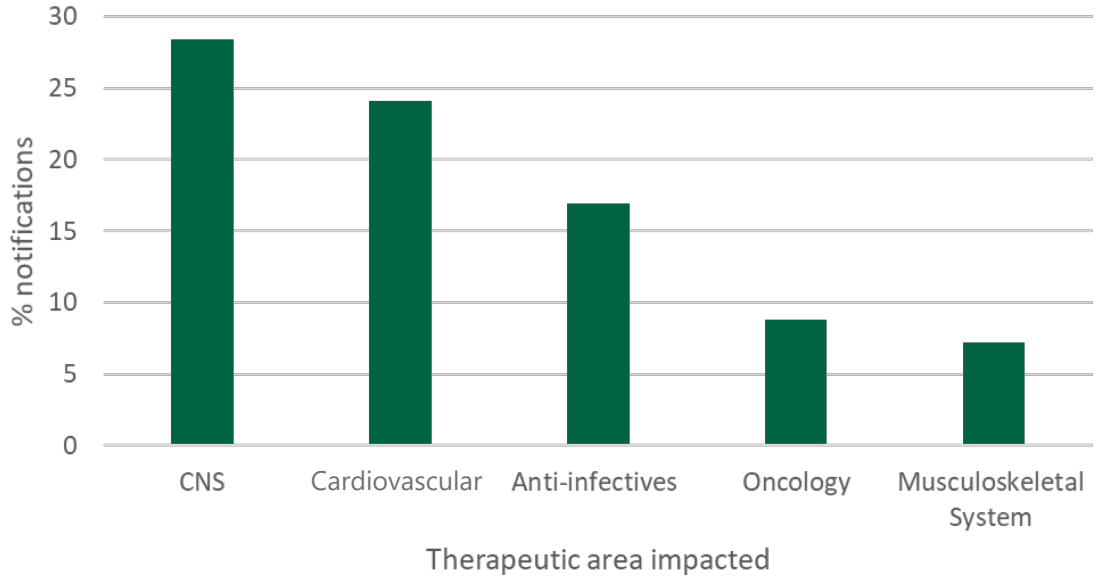
Source of first notification





Shortages Two year review data

Therapeutic area impacted



Class (Level 1 %)	Central nervous system (N, 22%)	Cardiovascular system (C, 14%)	General anti-infectives (J, 12%)	Alimentary tract & metabolism (A, 10%)	Antineoplastic & immunomodulating agents (L, 7%)
Subclass (Level 2, %)	pain relief (N2, 25%)	Antihypertensives (C2, 32%)	Systemic antibacterials (J1, 54%)	Antacids (A2, 25%)	Cytostatics (L1, 64%)

HPRA Website Searchable List

Medicines Shortages List

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Use the Search box to search for a specific product or active ingredient.

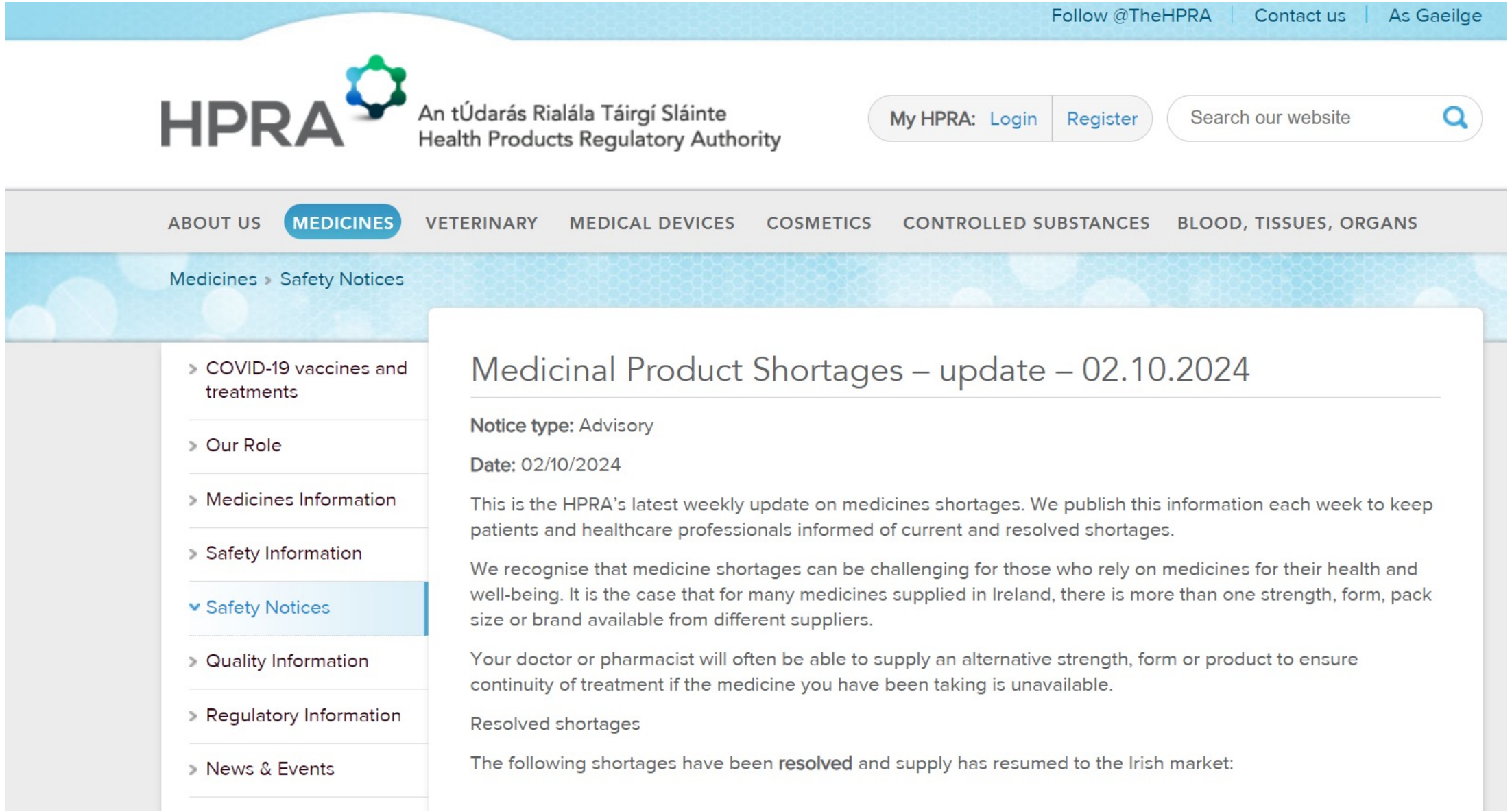
Alternatively you can use the arrows to sort alphabetically by product name / active ingredient or sort by date.

Search by product or active ingredient: cinac

Show 10 entries

Product name	Active ingredient	Therapeutic alternative	Reason	Date of shortage	Expected return date	Additional information	Last updated
Cinacalcet Accordpharma 30 mg film-coated tablets *EU/1/20/1429/001-004* Accord Healthcare S.L.U.	Cinacalcet	Exact alternative medicine authorized	Quality issue	2024/09/23	Awaiting update from company		2024/10/08
Cinacalcet Accordpharma 60 mg film-coated tablets *EU/1/20/1429/005-008* Accord Healthcare S.L.U.	Cinacalcet	Exact alternative medicine authorized	Quality issue	2024/09/23	Awaiting update from company		2024/10/08

Weekly Update and Resolved List



Shortages framework
Options for mitigation

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- Determine impact
- **Proposal to address shortage**

Regulatory responses

Batch-specific request

Exempt Medicinal Product

Expedited variation for product

Expedited inspection/variation for manufacturer, wholesaler

Expedited CD import licence

Engage with other agencies

Wider stakeholder responses

Increased supply of alternative generic, strength or form

Increased supply of appropriate alternative

Equitable distribution practices

Reimbursement codes or hardship arrangements

Clinical guidance from HSE/MMP

Communication responses

Patient groups

Pharmacists

Doctors

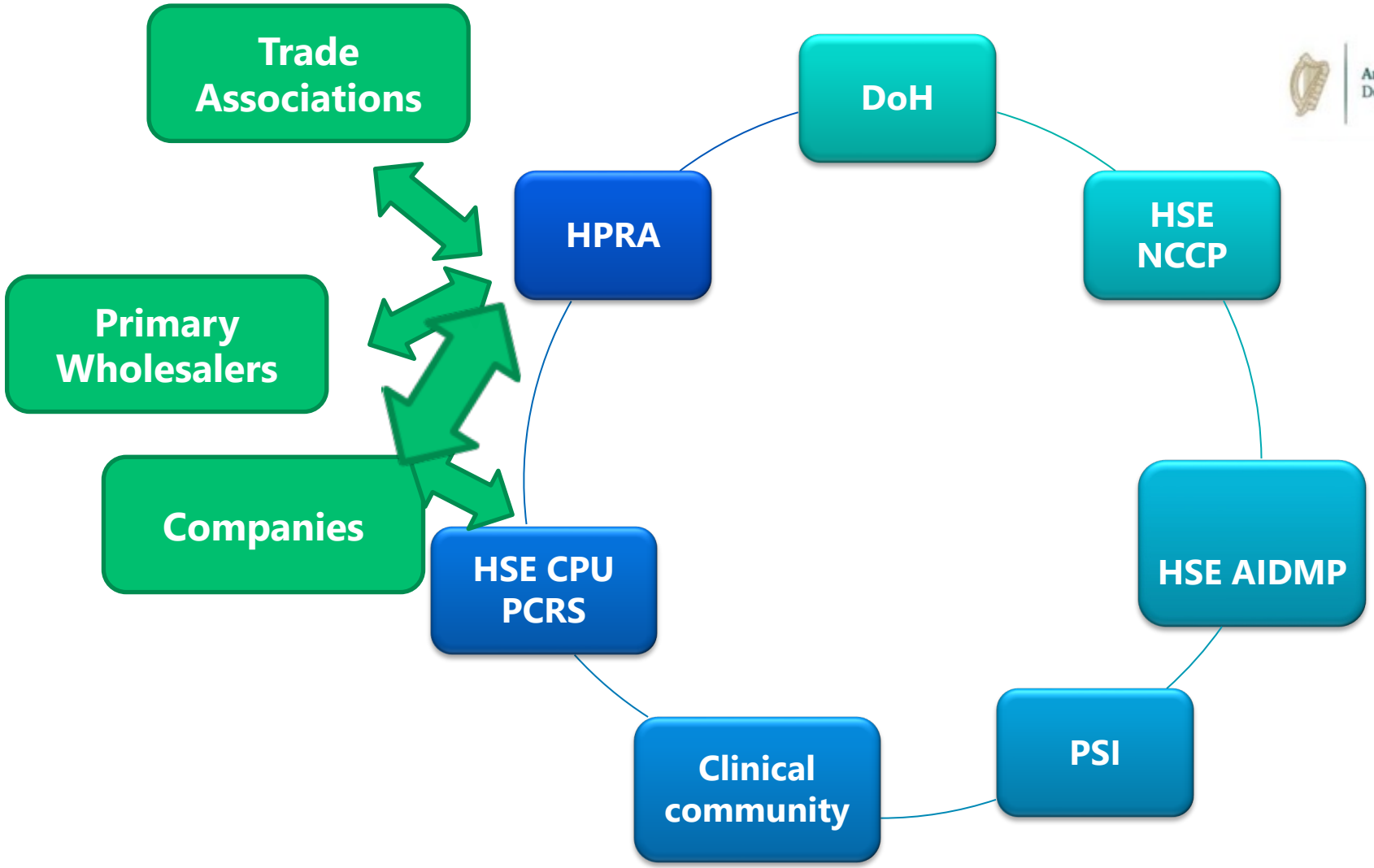
Hospitals

Website DHCP Guidelines

Practical Example Pabrinex®-MCAG

- HPRA Notified of High Impact Shortage Pabrinex® IV High Potency Concentrate for Solution for Infusion, due to a manufacturing issue, impacting multiple countries
- Pabrinex® IV licensed in adults for rapid therapy of severe depletion or malabsorption of the water soluble vitamins B and C, particularly in alcoholism where a severe depletion of thiamine can lead to Wernicke's encephalopathy
- The shortage was expected to impact Ireland from September 2024 until Q3 2025
- The Medicines Criticality Assessment Group was convened to consider the shortage

Medicines Criticality Assessment Group (MCAG)



Practical Example Pabrinex®

- Output of MCAG:

1. HSE led stakeholder engagement within clinical groups
2. HSE Published Clinical Recommendations (led by AIDMP/AHDMP)

MAH mitigation strategy:

- MAH put allocations in place in partnership with their wholesaler at wholesale level based on average historical demand
- Due to rationalisation and conservation strategy the shortage is now expected to occur February 2025

Medicines Shortages List

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Use the Search box to search for a specific product or active ingredient.

Alternatively you can use the arrows to sort alphabetically by product name / active ingredient or sort by date.

Search by product or active ingredient: pabri

Acute Hospitals Drug Management Programme (AHDMP), National Clinical Programmes for Gastroenterology & Hepatology, Emergency Medicine and Neurology

Show 10 entries

Product name	Active ingredient	Additional information	Last updated
Pabrinex Intravenous High Potency Concentrate for Solution for Infusion *PA2288/001/001* Kyowa Kirin Holdings B.V.	Ascorbic acid, riboflav pyridoxine, nicotinam thiamine & glucose	HCP letter HSE clinical advice	2024/07/15

HSE Recommendations for Pabrinex® and Thiamine Prescribing due to International Supply Disruption of Pabrinex® IV High Potency Concentrate for Solution for Injection – July 2024

Previous1Next

Practical Example Fluenz®- Regulatory Flexibility

- Fluenz nasal spray suspension Influenza vaccine (live attenuated, nasal) potential shortage notified 2nd October to impact 17th October
- No alternative medicine authorised
- 2-17 year old children being vaccinated as part of the Health Service Executive (HSE) Seasonal Influenza Vaccination Programme for 2024/2025
- Company proactively engaged with HSE NIO and HPRA
- HPRA Human Products Authorisation & Registration (HPAR) team received an aplication for BSR of Italian stock 3rd October

Medicines Shortages List

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Search by product or active ingredient: fluen

Show 10 entries

Product name	Active ingredient	Therapeutic alternative	Reason	Date of shortage	Expected return date	Additional information	Last updated
Fluenz nasal spray suspension Influenza vaccine (live attenuated, nasal) *EU/1/24/1816/002* AstraZeneca AB		No alternative medicine authorised	Shipping delay/distribution issue	2024/10/17	2024/10/30		2024/10/03

Previous1Next

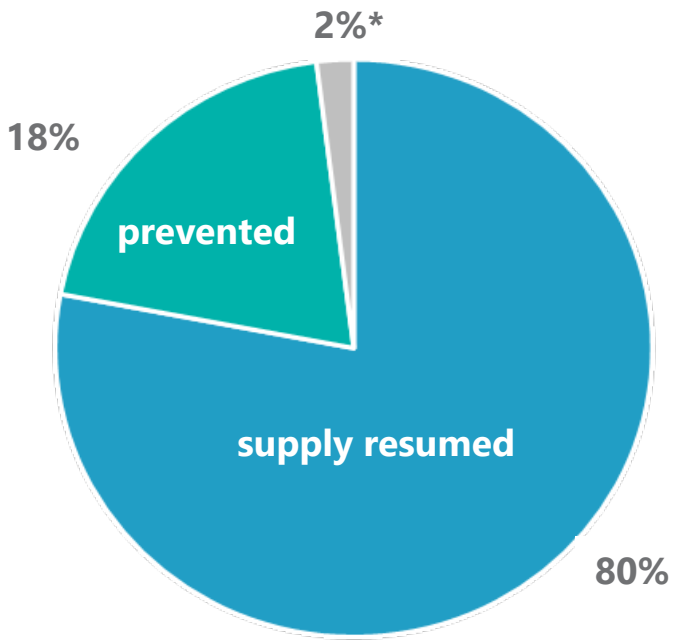
HPRA Batch Specific Requests

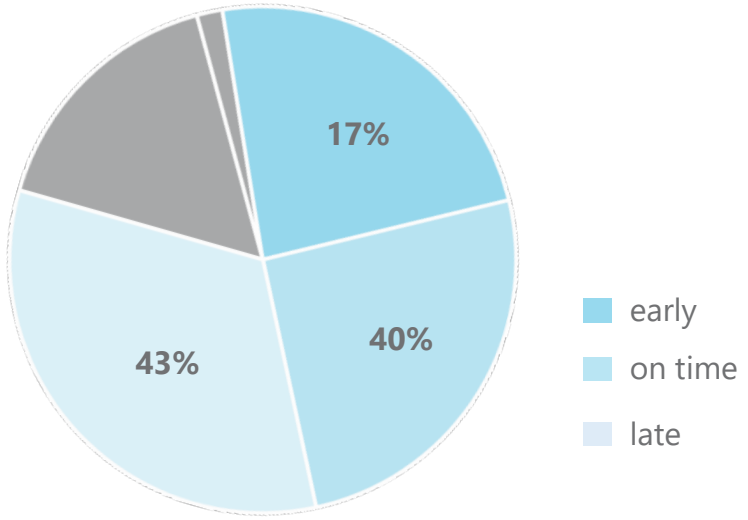
- Batch-specific requests (BSR) are accepted for critical medicines which hold a marketing authorisation issued by HPRA or by the European Commission to bring a batch of product into compliance with its marketing authorisation
- HPRA can facilitate BSR to ensure maintenance of supply of medicines
- BSR are limited in duration (normally no longer than three months) and can only be submitted for authorised medicines
- HPRA Guide to Batch-Specific Requests for Human Medicines available online

Practical Example Fluenz®

- HPRA Shortages team engaged with HSE NIO
- HPRA Human Products Authorisation Registration (HPAR) team approve request for BSR of Italian stock 4th October
- HSE NIO communication to all sites/vaccination sites who receive the vaccine notifying them of the BSR Italian packs via National Cold Chain Service
- Company email 4th October outlining BSR has averted the potential shortage

Shortages resolution





* indicates products were discontinued

HPRA Coordination role

The HPRA's regulatory remit does not extend to:

- Pricing and Reimbursement
- Operation or Negotiation of Pricing Frameworks
- Commercial issues
- Sourcing medicines/Purchasing medicines
- Clinical guidance
- Compelling a company to produce a medicine or increase production
- Compelling a company to apply for a marketing authorisation

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recommendations

8

optimisation of current system

prevention and mitigation strategies

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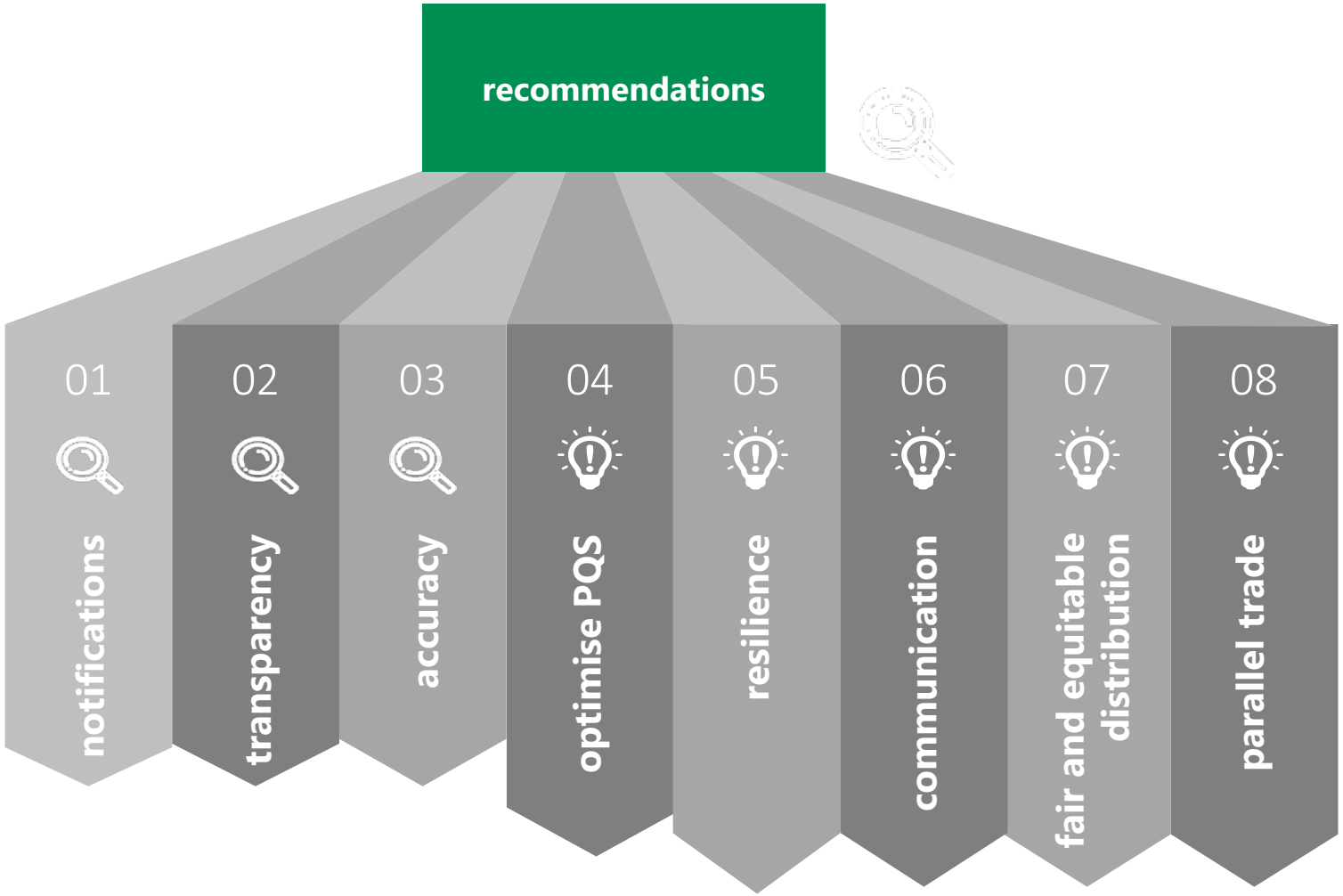
Medicinal Product Shortages
Two-Year Review

July 2022



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Medicine Shortages

EMA expanded mandate and EU strategy

Legislation

- **Directive 2001/83/EC obligations on continued supply (Article 81)**

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.

- **Regulation EU 2022/123**

Regulation 2022/123

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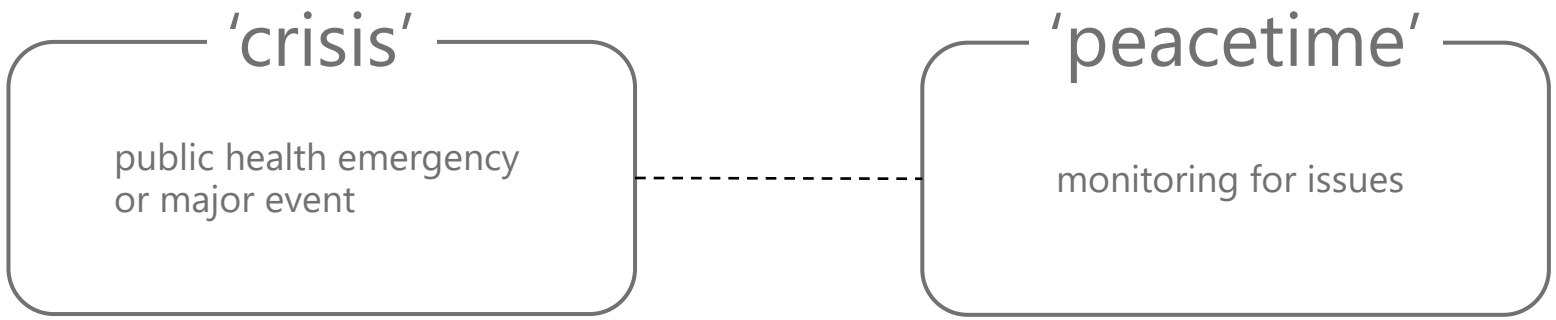
REGULATIONS

REGULATION (EU) 2022/123 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 25 January 2022

on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices

(Text with EEA relevance)



European activities focused on shortages

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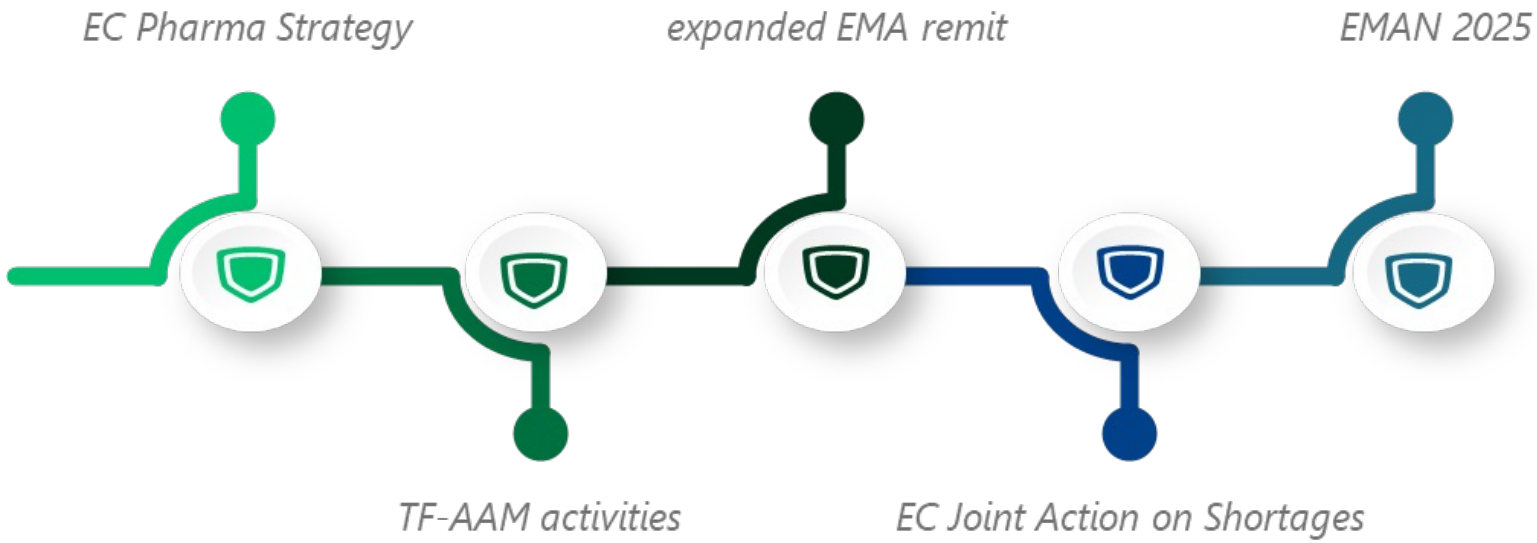

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HMA
Heads of Medicines Agencies

European Commission

European activities focused on shortages

- European Commission's Pharmaceutical Strategy, where part of the work focuses on improving supply chain resilience
- The joint task force of the Heads of Medicine Agency EMA on the availability of medicines, which will progress strategies aimed at shortage prevention
- The further development of the European Medicinal Product Single Point of Contact (SPOC) Working Group, facilitating greater communication on shortages that may impact multiple countries
- The introduction of legislation to expand the remit of the EMA to enhance coordination of shortages from an EU perspective,
- The European Joint Action on shortages and the inclusion of medicine shortages in the European Medicines Agencies Network Strategy to 2025

European Medicines Agency (EMA)

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- EMA publishes information on critical shortages monitored at EU level by the Medicine Shortages Single Point of Contact (SPOC) Working Party
- EMA formally established the SPOC Working Party in May 2022 in accordance with the Regulation on EMA's Reinforced Role (Regulation (EU) 2022/123
- SPOC-WP minutes available online
- Information on critical shortages available

Examples of shortage information on EMA website

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An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

5 July 2024
EMA/169758/2024

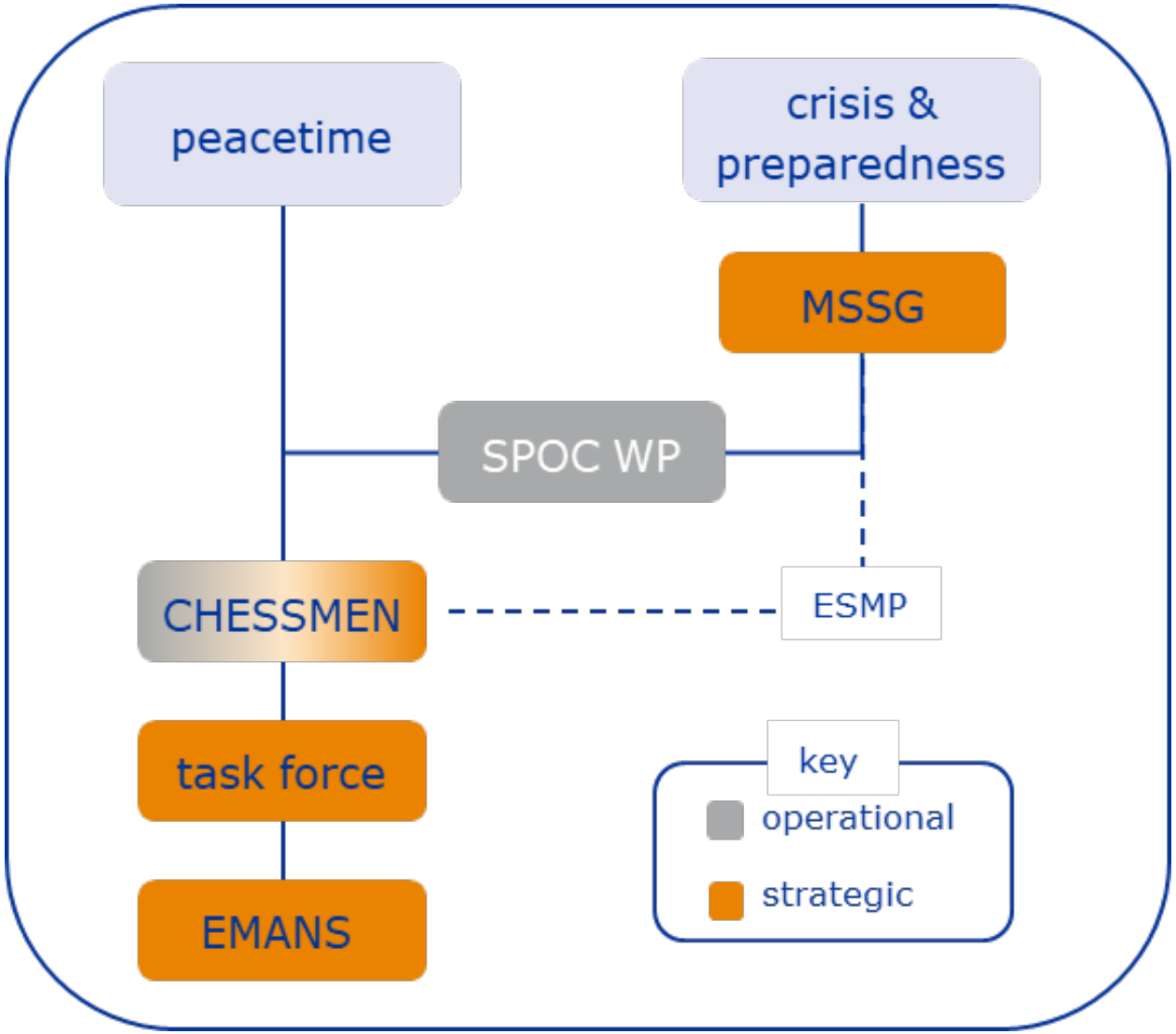
Shortage of Zypadhera (olanzapine) Powder and solvent for prolonged-release suspension for injection (210 mg, 300 mg and 405 mg)	
What is Zypadhera used for?	Zypadhera is used to maintain the improvement of symptoms in patients with schizophrenia who have already been stabilised on an initial course of olanzapine taken by mouth. For further information on the use of the medicine please refer to the medicine's overview page.
Reason for shortage	The company making Zypadhera is experiencing manufacturing problems with the 50 mm needles provided with the medicine for the injection. This has led to supply constraints and intermittent shortages of all Zypadhera strengths. The shortage is not related to a quality defect of the product or a safety issue. In order to reduce the impact of the shortage on patients, Zypadhera will temporarily be distributed with three 38 mm safety needles instead of two 38 mm and two 50 mm safety needles.
Member States affected	The shortage affects all EU/EEA Member States where the product is marketed. This information may change. For up-to-date information about the status of a medicine shortage in a particular Member State, consult the national shortage register or contact the national competent authority.

Examples of shortage information on EMA website

15 April 2024
EMA/91157/2024

Shortage of Creon (pancrelipase/pancreas powder) hard capsules for oral use (10,000, 25,000 and 35,000 units)	
What is Creon used for?	Creon (also marketed as Kreon in certain Member States) contains pancreas enzymes (lipase / amylase / protease) and is used to treat pancreatic exocrine insufficiency (a condition in which the pancreas insufficiently delivers digestive enzymes into the small intestine, thereby preventing food from being fully digested) resulting from other conditions or ageing.
Reason for shortage	The company that produces Creon is experiencing limitations in production capacity. Coupled with a high demand, this has led to intermittent shortages in the supply of Creon hard capsules. The shortages are not related to a quality defect of the product or a safety issue. Production capacity limitations are expected to be resolved in the second half of 2026. Until then, periodic shortages in the supply of Creon are anticipated.
Member States affected	The shortage affects some of the Member States where the product is marketed: Austria, Belgium, Bulgaria, Cyprus, Czechia, France, Greece, Italy, Ireland, Latvia, Luxembourg, Malta, Netherlands, Portugal, Spain and Sweden. This information may change. For up-to-date information about the status of a medicine shortage in a particular EU/EEA Member State, consult the national shortage register or contact the national competent authority.

Interplay of European activities related to shortages



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Medicine Shortages

Recent Legislative amendments and Future National Strategy

Health (Miscellaneous Provisions) Bill 2024

Reporting of information to support the security of supply of medicines

32I. (1) The Health Products Regulatory Authority may require a relevant person to provide to the Authority, in such form and manner and within such period as may be prescribed by regulations made by the Minister, such information in relation to medicinal products within the possession or control of the relevant person as the Authority considers necessary for the purpose of the management of the availability of medicinal products in the State, including—

(a) the monitoring of the current and future supply of medicinal products, and

(b) the identification and management of medicinal product shortages.

(2) A relevant person shall comply with a requirement set out in regulations made under subsection (1).

Health (Miscellaneous Provisions) Bill 2024

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(3) In this section, 'relevant person' means the following persons involved in the manufacture or supply of a medicinal product:

(a) the holder of a manufacturer's authorisation granted under Regulation 8 of the Medicinal Products (Control of Manufacture) Regulations 2007 (S.I. No. 539 of 2007);

(b) the holder of a marketing authorisation granted in accordance with the Medicinal Products (Control of Placing on the Market) Regulations 2007;

(c) the holder of a community marketing authorisation within the meaning of the Medicinal Products (Control of Placing on the Market) Regulations 2007;

(d) the holder of a wholesaler's authorisation granted under Regulation 9 of the Medicinal Products (Control of Wholesale Distribution) Regulations 2007 (S.I. No. 538 of 2007);

(e) a retail pharmacy business within the meaning of the Pharmacy Act 2007;

(f) a hospital;

(g) such other persons or legal entities, being persons or entities authorised or entitled to supply medicinal products, as may be prescribed in regulations made by the Minister.".

Future of the Framework: Management of Medicines Availability??

- Enhanced governance (Aim to **build greater resilience** in national medicines supply and to enhance the current governance model for medicines availability)

- Development of **digital infrastructure** (Aim to develop a national digital system allowing for automated monitoring of medicines stock levels which would enhance the ability of the health system to track the availability of medicines in the supply chain). Better **forecasting of availability** and a greater capacity to model demand and supply.

- National legislation to align with EU strategy. **Mandatory requirement** for industry to provide notification of potential and actual shortages. Provision to request supply chain transparency. Health (Miscellaneous Provisions) Bill 2024

Any questions?