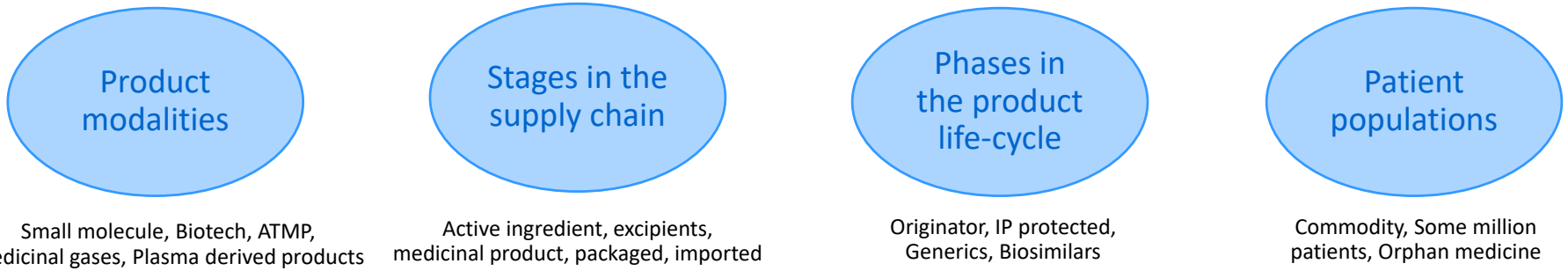
Session 3: Prevention of shortages

Dr.-Ing. Stephan Rönninger on behalf of industry

Setting the scene

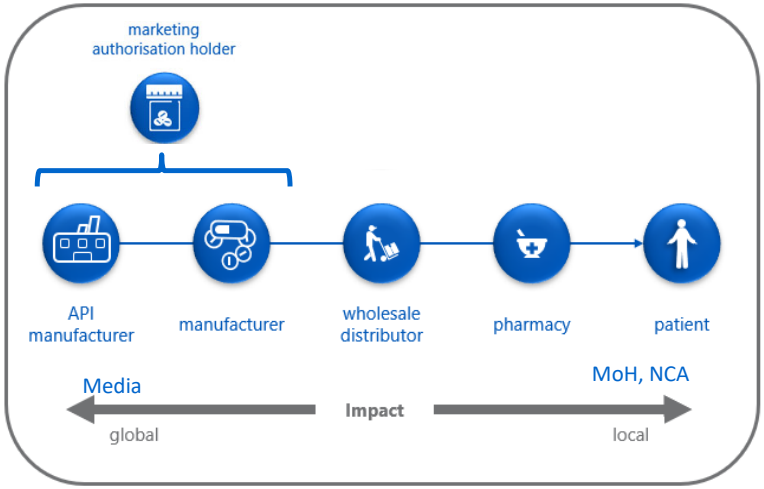
- **Prevention is essential**
  - Industry stakeholders have demonstrated continuous improvement with the help of regulators
  - Immediate actions in case of health and other crises
    - Prevented stock outs, or
    - From getting worse due to increasing demand
- **There is the need for different 'best practice' solutions**



Feedback on EMA's Good Practice Guideline

- **Stakeholders and their role in the supply chain**
  - Can there be <u>one</u> list for 'critical medicines' and <u>one</u> reporting system across EU?
  - What is the role of geopolitical factors and the influence from media?
  - How does every stakeholder realise their influence?
    Consider e.g.,
    - Unintended consequences of any action taken
    - The inter-related environment
    - Focusing on the need of the patients

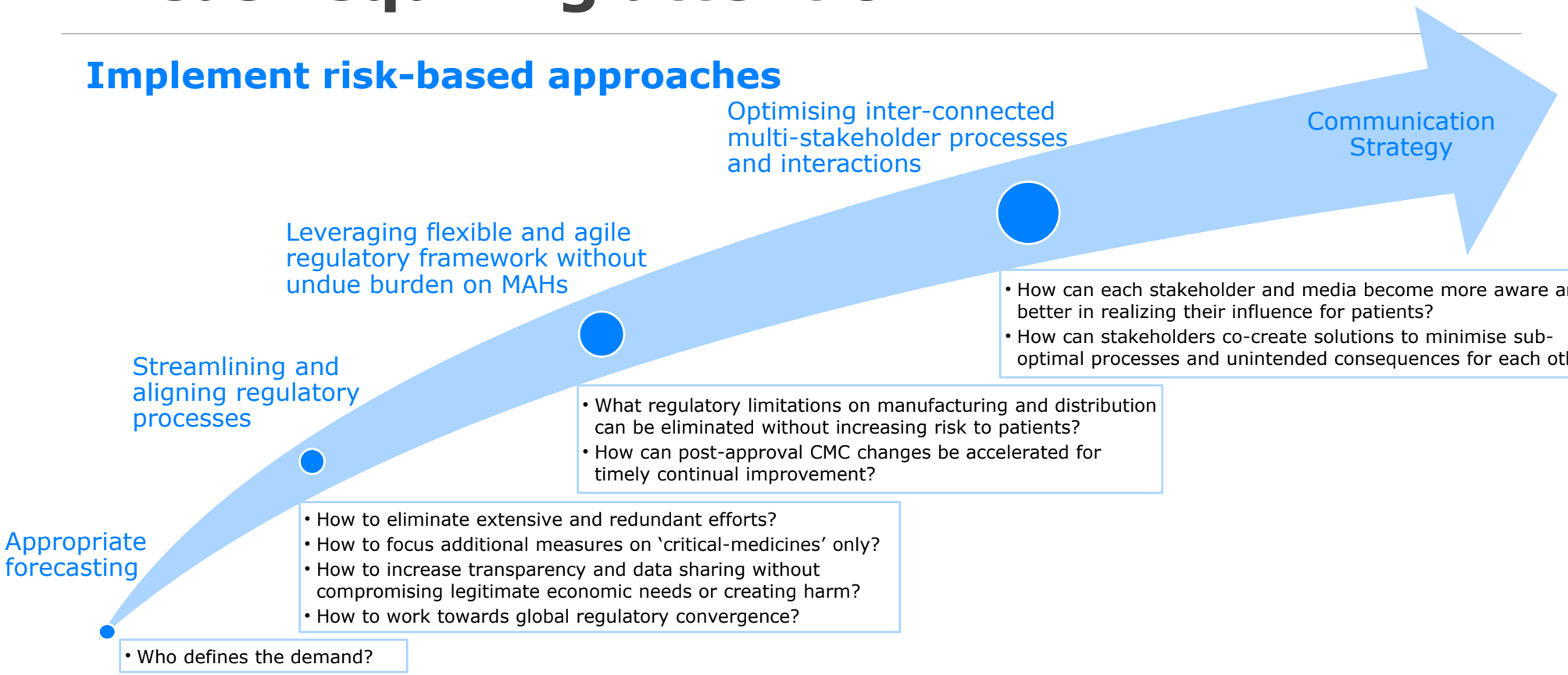
- **The MAH is not able to fulfil the responsibility alone**
  - How can the Marketing Authorisation Holder (MAH) get information after manufacturing?
  - How can industry achieve more visibility on the 'demand'?



Potential modification of the graphic from page 4 of the Good Practices draft guideline, EMA/760980/2022, 21 October 2022; shared with stakeholders

Areas requiring attention

Implement risk-based approaches

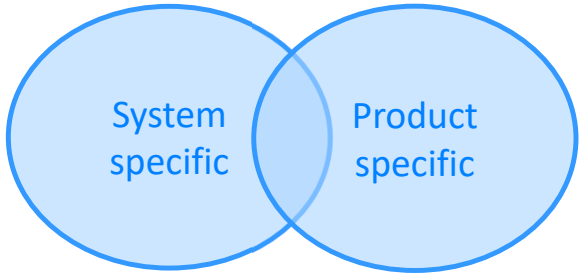


Update on ongoing or planned industry initiatives

- **Manufacturing capacities to strengthen Europe's resilience**
  - Securing and diversifying global supply chains with an enhanced internal and contracted manufacturing footprint in Europe

- **Drug shortage prevention plan established based on a risk-based approach**
  - How can <u>one</u> template be applied all over Europe per stage in the supply chain?
  - How can we focus on 'critical' medicinal products only and share with regulators?

- **'Best practice' tools are**
  - Available
  - Trained
  - Maintained



*Risk-based approach for prevention and management of Drug Shortage Open access & further Drug Shortages Initiative, for trainnig see e.g., PDA, ISPE

From stakeholder-focused to patient-centered

Holistic, multi-stakeholder

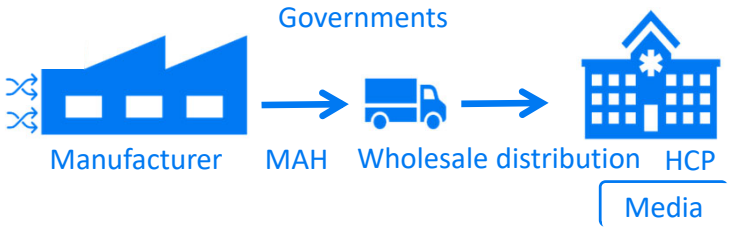
Transparency

Science & risk-based approach

Requirements

Each stakeholder shall realise their influence

Solutions



Fit for purpose

Additional Details

Abbreviations

Abbreviation	Stands for
API	Active Pharmaceutical Ingredient
ATMP	Advanced therapy medicinal products
CMC	Chemistry. Manufacturing, Control
ECDC	European Centre for Disease Control
ESMP	European Shortages Monitoring Platform, provided by EU Regulation 2022/123
ICH	International Council of Harmonisation
IP	Intellectual property
MAH	Marketing Authorisation Holder
MoH	Ministry of Health
NCA	National Competent Authority
PDMP	Plasma Derived Medicinal Product
RUP	Repeat Use Procedure
SPP	Shortage Prevention Plan

Drug Shortage Prevention

Participating Associations

Logo	Abbreviation	Stands for	Link
	-	Affordable Medicines Europe	https://affordablemedicines.eu/
	EIGA	European Industrial Gases Association	https://www.eiga.eu/
	EIPG	European Industrial Pharmacists Group	https://eipg.eu/
	EFPIA	European Federation of Pharmaceutical Industries and Associations*	https://www.efpia.eu/
	EUCOPE	European Confederation of Pharmaceutical Entrepreneurs	https://www.eucope.org/
	EuropaBio	European Association for Bioindustries	https://www.europabio.org/
	GIRP	European Healthcare Distribution Association	https://www.girp.eu/
	ISPE	International Society for Pharmaceutical Engineering*	https://www.ispe.org/
	-	Medicines for Europe	https://www.medicinesforeurope.com/
	PDA	Parenteral Drug Association*	https://www.pda.org/
	PPTA	Plasma Protein Therapeutics Association	https://www.pptaglobal.org/
	VE	Vaccines Europe	https://www.vaccineseurope.eu/

*Prevention of drug shortages based on quality and manufacturing issues, EMA & Inter-Associtaion team, 2014, link

Drug Shortage Prevention

EMA draft guidance on shortage prevention

Proposed best practices recommendations for drug shortage prevention

1. Notify the NCA of a potential or actual shortage as soon as possible in advance of any shortage
2. Increase transparency relating to shortage information.
3. MAHs should increase the accuracy of notification detail provided.
4. All actors* should each have a shortage prevention plan specific to their role.
5. All actors* should each have a shortage management plan to respond to issues resulting in shortages
6. Optimise PQS to strengthen the reliability and resilience of supply chains throughout the lifecycle of a medicine
7. Increase resilience in the supply chain, taking into account known vulnerabilities
8. Improve communication between stakeholders
9. Promote fair and equitable distribution to meet the needs of patients
10. Take appropriate steps to minimise the risk of parallel trade or export exacerbating shortages

*Links to such actors in the supply chain to be e.g., MAHs, manufacturers and wholesalers

Draft Good practices for the prevention of human medicinal product shortages, EMA/760980/2022, 21 October 2022, draft shared with stakeholders

Key points by associations

Associations in alphabetical order

SUPPORT

- The purpose of the guidance
- Using the EMA/HMA definition of shortages
- Recommendations 1, 2, 3, 6, 7 and 9.

- Suggest to include an 11th recommendation:

NCAs should together with the relevant import stakeholders establish a national process for fast-track parallel imports (fast-track licensing process) or unlicensed imports.

CONCERNS

- R4 & 5: Prevention and management plans are primarily useful tools for those in control of production, so limit to MAHs.
- R8: we propose a more active role for the NCA's here as an interlocutor – not least to overcome competition concerns.
- R10: We agree exports should not cause not exacerbate shortages – but the proposed wording of R10 is unacceptable in relation to the definition of parallel trade, the reference to shortage definition, as well as potential anti-competitive recommendations on company behaviour. We have proposed an amended text, that should fulfil the wish of NCA's, while respecting the rules, case-law, and commonly accepted definitions.

European Industrial Pharmacists Group
Groupement des Pharmaciens de l'Industrie en Europe

Shortage prevention plan

1. Establish pro-active risk management plan
2. Prepare list of medicinal products of clinical importance that lack therapeutic alternatives
3. Undertake regular checks on market availability of alternative products especially those with low pricing due to cap measures
4. Criticality in the procurement of all starting materials with particular attention to APIs
   - How to mitigate?
5. Quality and manufacturing aspects that could have an impact on medicines' shortages
   - How to manage them preventively?
6. Appropriate agreements on quality and capacity of CMOs
7. Need to review quality management systems throughout life cycle (including those for older products)
8. Consideration of batch release and transportation impact on the time to deliver products to the market
9. Review impact on production planning of potential weaknesses in sales forecasting

Shortage prevention policy: a long journey with already some achievements

Achievements	Comments
Common SPP template (PDA-approved and in line with EMA guidance)	Limit mandatory use to critical medicines only Available upon request Updated version available by mid-2023
Common reporting system enshrined in EU regulation (ESMP under way)	Ensure full interoperability with existing databases and platforms Avoid duplication with Member States requirements (source of errors, burdensome)
Use of regulatory flexibilities during pandemic	Targeted use of flexibilities have proven useful to improve availability of medicines during the COVID-19 pandemic. They could be made available when required by the situation.

EFPIA-MfE-VE Shortage Prevention

Key industry proposals to address shortages (1/2)

Harmonised EU shortage prevention framework

- Common definition of a shortage (with a definite timing), harmonised shortages reporting, common, interoperable IT framework, European approach on Medical Counter Measures (MCM)

Increased transparency in the Supply Chain

- Improved transparency and understanding of patient demand through timely (current and forward looking) epidemiological data, including during health crisis shared by the European Centre For Disease Control (ECDC)
- More transparency in the supply chain for (national and EU) competent authorities, including through the use of available data, e.g. EMVS

Risk-based approach
for an efficient shortage prevention mechanism (put resources where the needs are, level of effort commensurate to level of risk, as stated in ICH Q9)

- Focussed critical medicines list at EU level (updated upon need). Risk assessed according to i) therapeutic indication of the medicine ii) availability of adequate alternatives and/or resilience of the supply chain
- Special measures applying to critical medicines, e.g. Shortage Prevention Plans (SPPs), safety stocks…

EFPIA-MfE-VE Shortage Prevention

Key industry proposals to address shortages (2/2)

Rational use of regulatory flexibilities, e.g.	• Facilitate use of another EU-pack in a different country, including by accelerating the replacement of the paper leaflet by electronic product information • Quick approval of variations, enabling efficient RUPs, and fast-track API changes
Harmonisation and simplification across Europe	• EU Common pack for vaccines • Greater use of multilingual packs • Harmonisation across Member States (fewer different packaging, fewer formulations) and "EU" packs

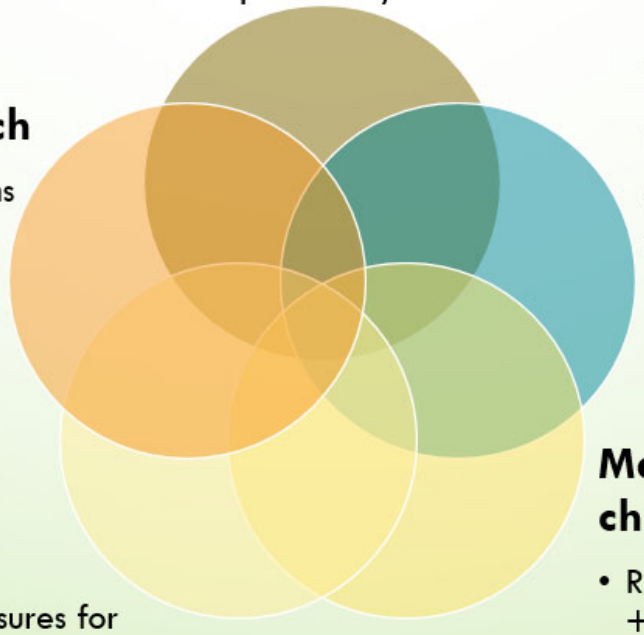
Note: Detailed EFPIA comments to the *EMA Draft Good practices for the prevention of human medicinal product shortages* are available **here**. https://efpia.box.com/s/rr3sy57bqpb91hd23z8s3bmeukwctvp0

EFPIA-MfE-VE Shortage Prevention

Industry proposals to prevent and mitigate shortages

EU shortage system

- Common definition
- IT interoperable system



Risk-based approach

- Shortage Prevention plans
- Safety stocks

Transparency-based resilience

- Use of EMVS data
- Patient demand

Flexibility

- Regulatory mitigation measures for shortages

Maintain resilient supply chains

- R&D and manufacturing capacity + open global supply chain
- Targeted incentivisation that do not discriminate

Abbreviations

- API: Active Pharmaceutical Ingredient
- ECDC: European Centre for Disease Control
- EFPIA: European Federation of Pharmaceutical Industries and Associations
- EMVS: European Medicines Verification System
- ESMP: European Shortages Monitoring Platform, provided by EU Regulation 2022/123
- MAH: Marketing Authorisation Holder
- MfE: Medicines for Europe
- PDA: Parenteral Drug Association
- RUP: Repeat Use Procedure
- SPP: Shortage Prevention Plan
- VE: Vaccines Europe

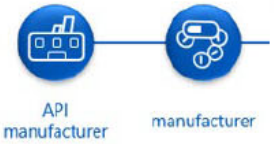
Typical supply chain overview / related risks for shortages

Medium risk
Personnel

- Remote release (where it is not allowed)
- Increased need of personnel for production and deliveries
- Including home care deliveries

marketing authorisation holder

Low risk
Generally also manufacturer and distributor and sometimes also API manufacturer



API manufacturer | manufacturer

Low risk
Locally, generally close to the customers, generally within the EU

Low to Medium risk
Gasous (cylinders) or liquid (dewars) supply to hospitals
→ high increase in demand, may lead to availablity problems for related equipment e.g. cylinders, dewars, valves and pressure regulators

Low risk
Liquid supply to hospitals

Medium risk
Gasous (cylinders) or liquid (dewars) supply to home care patients
→ high increase in demand, may lead to availablity problems for: related equipment e.g. cylinders, dewars, valves and pressure regulators

Medium risk
Medicinal gas (especially oxygen) distribution systems in hospitals may not be equipped to satisfy the increases in demand (outside the responsability of medicinal gases manufacturers)
→ will lead to increases in demand of cylinders, dewars, valves and pressure regulators

CONCLUSIONS

- EIGA members would like to thank EMA and the national competent authorities for the good communication during the unfortunately still ongoing COVID-19 pandemic.
- As result there were no shortages of the medicinal gases molecules through the pandemic, also during the peaks of COVID-19 pandemic, because the regulatory flexibility adopted allowed to effectively face any lack of packages, medical manufacturing staff, Qualified Persons and other unnecessary limitations on manufacturing and distribution (also across borders). We believe that the proposed regulatory flexibilities (see our BN 25 www.eiga.eu), that most EU Member States adopted in full, would be best to be transformed into permanent regulations, just to be activated in case of need, to quickly respond to a rapid increase in demand and to limit the factors contributing to potentially putting the patients and healthcare facilities at risks.
- We also see that the limitations in supply are not always in the responsibility of the marketing authorisation holder and/or manufacturer as some medicinal gases, like oxygen, are distributed over a medical gas pipeline system in the hospital which is designed only cover certain demand and cannot be increased without major modifications. Also this must be taken into account when dealing with a preparedness for future crisis situations.

EUCOPE contribution

Streamlining and concerted regulatory measures can support in the prevention and mitigation of shortages

- **Establishing a close dialogue is key**
  - Industry (MAH) – Health Authorities – EU Commission
- **Increase intra-EU countries drug information (EU community of 27MS, common labeling)**
  - Centralize common labeling text approach existing for CP but not for MRP/DCP procedure (limit HA country requirement)
  - Prioritize digital labeling (ePI) implementation (EU ongoing initiative and legislation change)
- **Policy coordination and information exchange between regulators**
  - Avoid siloed decisions / country by country (one common stock out repository in EU)
  - Align on common definition of shortage and reporting rules - mainly for critical products
  - Establish early alert system (EU) to rapidly identify potential disruption and reallocate product where supply is needed
- **Regulatory flexibility for post-approval changes**
  - Increase the predictability and efficiency of post approval changes to reduce risk of drug unavailability (e.g., ICH Q12 full adoption)

1

EuropaBio shortages – key messages

- EuropaBio considers that increasing biomanufacturing capacities in Europe as well as securing and diversifying global supply chains are essentials to strengthen Europe's resilience against shortages. It is important to address shortages through the biopharmaceutical value chain.
- Streamlining communication channels to avoid duplication with Member States reporting requirements and unnecessary burden on MAHs is necessary to leverage a flexible and agile regulatory framework in order to be more efficient in the life cycle management of CMC changes.
- In 2022, EuropaBio launched its Biomanufacturing Platform to address the policy and wider frameworks through which biomanufacturing is delivered.

GIRP recommendations for shortages prevention

1. Implementing the definition of medicines shortages in Regulation (EU) 2022/123 into national law for all medicines
2. EU-wide harmonised categorisation of root causes of shortages
3. Exhaustive mapping of the global supply chains for medicines, including raw materials, APIs, auxiliary products, etc;
4. Shortages prevention plans by manufacturers as well as shortages management plans by all supply chain stakeholders
5. Legal basis for an EU-wide early warning system for potential and verified/confirmed shortages for critical medicines, involving all supply chain stakeholders
6. Revision of the wholesale distribution licensing system, differentiating pharmaceutical full-line wholesalers from other operators by law
7. Implementing a right for full-line wholesalers to be adequately and continuously supplied" by pharmaceutical manufacturers, enforceable by NCAs.

GIRP

ISPE Drug Shortage Prevention Model

- Drug shortage prevention is multi-faceted and excellence is achieved through sustained accomplishment in many areas of pharmaceutical manufacturing
- Evolving Regulations/Global harmonization is particularly essential:
  - to allow flexibility in change management to prevent unnecessary drug shortages (*i.e.,* production site change for API or Drug products).
  - to improve drug shortage definitions and approaches for reporting and risk management planning

Quality and Manufacturing Maturity

- Pharmaceutical Quality System
- Cultural Excellence
- Workforce Capability
- Supply and Disruption Resilience
- Risk Management Planning
- Data Analytics

Technology & Innovation

- Advanced technology
- Digital Solutions
- Sustainability
- Life cycle management

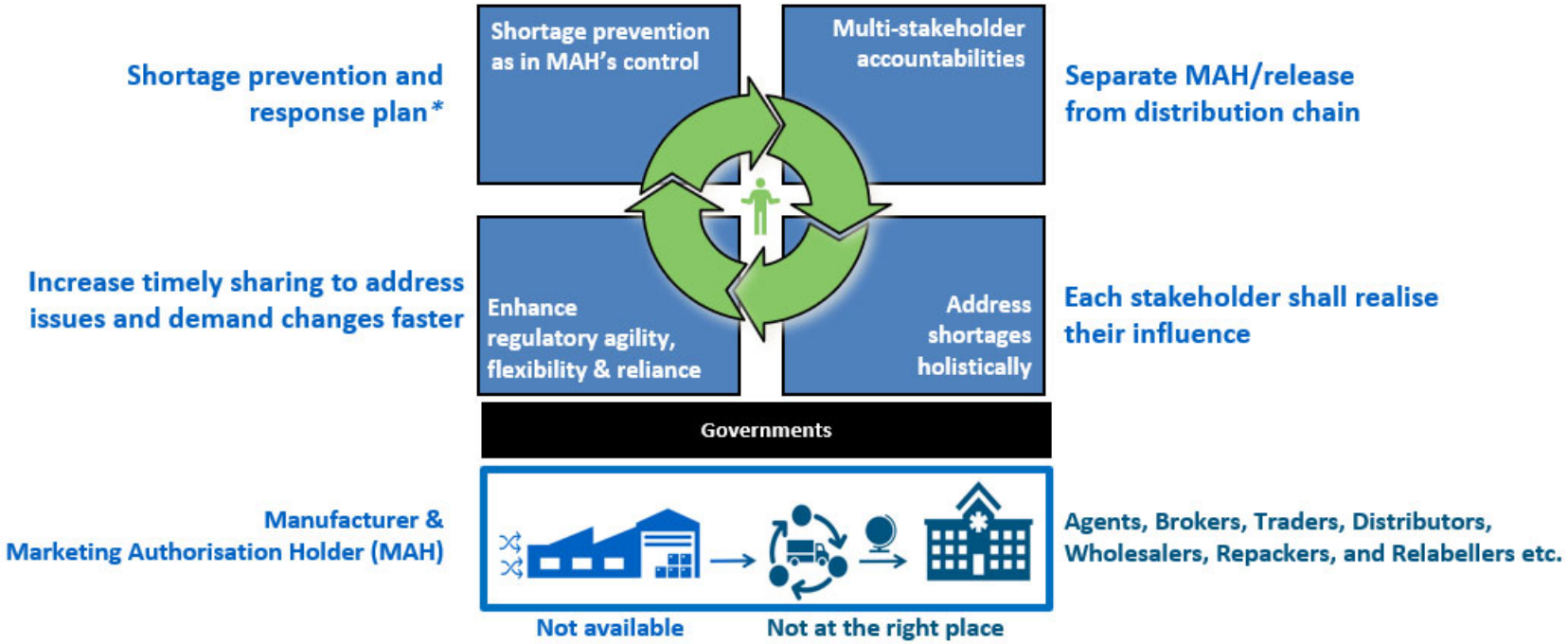
Regulatory

- Regulatory Execution
- Evolving Regulations

ISPE.

Connecting Pharmaceutical Knowledge

Management of Drug Shortages need Holistic, Multi-stakeholder, Science & Risk-Based Approaches

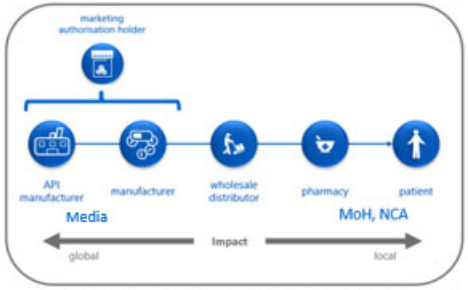


Patient-centered instead of Stakeholder-focused

*Open access to PDA Technical Report No. 68 on *Risk-based approach for Prevention and management of Drug Shortage*

Suggested actions for next steps

- **Update on ongoing or planned initiatives**
  - Ongoing in the offer training and consolidate best practices on the tools
    e.g., Drug Shortage Prevention and Mitigation Plan (PDA TR 68)*, Quality Management System (ICH Q10), Quality Risk Management (ICH Q9(R1))
  - Mapping of stakeholder's impact, their typical decision and their impact on drug shortage prevention – joint effort with stakeholders
- **Areas requiring attention**
  - How are decision by stakeholders oriented by the need of the patients?
  - How can stakeholders become better aware of unintended consequences for patients?
  - How can each stakeholder get more efficient and realise their influence, including media?
- **High-level feedback on the draft guidance on shortage prevention**
  - A helpful summary
    - We suggest adding a reference to the tool of '*Risk-based approach for Prevention and management of Drug Shortage*' (PDA Technical Report No. 68)*
    - How does every stakeholder realise their impact and is considering unintended consequences of any action taken in the interrelated environment?
  - Definition of drug shortage
    - Who defines the 'demand' in the Member State?
    - How can demand be addressed for patient worldwide?
  - Players and their role in the supply chain
    - What is the role of politics in healthcare?
    - How about the influence from media?
  - The Marketing Authorization Holder (MAH) may not be able to fulfil the enterprise responsibility
    - How can MAH get reliable information on supply after the first economic customer?
    - Which parties are responsible for having and managing the information after the first economic customer?



Potential modification of the graphic from page 4 of the guideline

PPTA Key Messages

Plasma-derived medicinal products (PDMPs) are unique therapeutics, hence following considerations need to be taken into account when issuing any assessments, recommendations, or guidance related to PDMPs shortage preparedness and management:

- The patient need for plasma-derived therapies is the driver of the demand for plasma components
- PDMPs can ONLY be made with human donated plasma and volumes of donated plasma directly impact availability of the product
- Production is highly complex and costly, with the end-to-end process taking up to one year
- Sourcing of the starting material = human plasma donations, cannot be scaled-up quickly
  - Significant EU's dependency on the US Source Plasma collection (45%, >90% for HY-IGs)
- No alternative sourcing regions, which makes supply chain vulnerable to export restrictions or infectious disease outbreaks
- IG therapy led to a benefit of 11 quality-adjusted life years (QALYs) resulting in cost effectiveness of almost 30,000 euro per QALY*
- No alternative treatment/therapeutic options for certain patient groups (PID)

- **A streamlined EU reporting system for shortages provides a great opportunity to enhance access to medicines, but requires a harmonized, consistent and workable common EU standard for shortages reporting**
- **The existing shortage monitoring instruments and national reporting obligations should be considered before introducing new shortage monitoring and preparedness mechanisms (eg. plasma collection monitoring systems, EU PMF)**
- **To ensure resilient supply chains for PDMPs, a regulatory cooperation, particularly with the US, and a global regulatory convergence is necessary (ex. the EU-US MRA)**

PPTA

** van Wilder, Philippe et al. (2021) PloS one vol. 16,3 e0247941. 4 Mar. 2021*

Recommendations for plasma-derived medicinal products (PDMPs)

Policies to address access issues should consider the unique nature of plasma-derived medicinal products (PDMPs) and use appropriate instruments to address often product- specific challenges

How can EMA assist?

→ Streamline regulatory oversight and improve efficiency (e.g., PMF related processes)

→ Allow more predictable environment (incl. timelines, resources)

Inspections:

- Advocate for increasing EU MS GMP inspector's contingent at GDP/MP/IWG
- Expedite GMP inspections of plasma centres & PDMPs manufacturing sites
- Issue improved guidance for EU inspectors on harmonization of inspection practices
- Advance EU-US MRA for PDMPs manufacturing sites
- Consider implementation of risk-based approach to inspections of EU and US plasma collection centres

Shortages monitoring:

- Workable and user-friendly tool with a standardized data set for shortages reporting
- Single point of contact (SPOC) network to improve information sharing between Member States

How can industry assist?

- Ongoing efforts in increasing plasma collection (new donation centres) resulting in approx. 38% increase in plasma collected in the EU (4 Member States: DE, AT, CZ, HU) over the past 10years
- Increasing PDMP manufacturing (fractionation) capacity
- Production process shortened during COVID-19 (e.g., inventory hold reductions and logistics)
- Optimising Ig production: improvement in plasma processing increasing yield by approx. 60% from 2,5g/L to 4-4,5g/L

PPTA