

Prevention of Drug Shortages Based on Quality and Manufacturing Issues

Final Report

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A Collaborative Contribution to the
European Medicines Agency (EMA) and
their Inspectors Working Group (EMA-IWG)
by



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1. Executive Summary

This report is a summary of the response to the European Medicines Agency's (EMA's) request to industry to provide solutions to the global problem of drug shortages caused by manufacturing, quality and/or GMP compliance issues. The report summarises complementary and collaborative work performed by organisations with individual people membership (ISPE, PDA), as well as European pharmaceutical industry associations (EFPIA, EGA, PPTA, AESGP). The solutions developed and described in this report could enable a shift from reactive to proactive prevention of shortages at a system and product level, and address harmonised communication principles to Health Authorities for drug shortages.

In November 2012 EMA issued a Reflection paper on medicinal product supply shortages caused by manufacturing / Good Manufacturing Practice Compliance problems (EMA/590745/2012) as well as an Implementation Plan 2012-2015 (EMA/708575/2012). A workshop was held by EMA in October 2013 as part of the implementation plan, and the industry response was the creation of an inter-association task force in November 2013. Two complementary work streams were agreed with EMA. One, under the auspices of the trade associations EFPIA, EGA, AESGP and

PPTA, addressed communication principles. The other involved the individual member based associations of PDA and ISPE, who were chartered “To deliver to the EMA a proposal and plan that address the prevention of drug shortages due to “Manufacturing Quality Issues” and to support that plan through the activities of the contributing associations. The term “Manufacturing Quality Issues” is meant to “encompass quality defects, failure of the manufacturing process, non-compliance with EU GMP or other EU quality requirements”. This second work stream has resulted in two deliverables, namely a root cause-based prevention plan at a system level (ISPE), and a risk-based prevention plan at a product level (PDA). The inter-association team worked closely together and is now presenting an array of solutions that, when implemented, could help reduce drug shortages caused by manufacturing, quality and/or GMP issues. **It is important to note that manufacturing, quality and GMP compliance issues are only one subset of the many diverse root causes for shortages.**

The EFPIA, EGA, AESGP and PPTA “**Quality and manufacturing driven supply disruptions: industry communication principles to Authorities**” provides an opportunity for enhanced transparency and predictability of managing drug shortages through harmonised communication principles between industry and authorities, and a reporting framework with identical trigger point and time points for notification.

The ISPE “**Drug Shortages Prevention Plan (DSPP)**” describes a holistic system based approach to proactively prevent drug shortages through a framework focused on six dimensions- corporate quality culture, robust quality system, metrics, business continuity planning, communication with authorities and building capability. Companies can use the drug shortages prevention plan as a “reflection paper”, to help them look holistically across their entire supply chain, identify the potential gaps and define an appropriate action plan; they can use it also as a “tool-kit” and can benefit from the discussion points and the industry examples provided in each chapter.

The PDA Technical Report “**Risk-Based Approach for Prevention and Management of Drug Shortages**” is a productbased approach describing a risk triage model that can be used to assess drug shortage risks and implement appropriate controls in the end-to-end value chain for manufacturing and distribution of a product. Templates for a Drug Shortage Risk Register and a Drug Shortage Prevention and Response Plan are provided. Companies can use the Technical Report and the templates to systematically and proactively identify potential risks to product supply in the end-to end value chain for a product, prioritise risk mitigation activities and use the outputs to engage in proactive dialogue with health authorities.

The work presented by the inter-association task force represents the most comprehensive input to date to tackle the issue of drug shortages caused by manufacturing, quality and/or GMP compliance issues. Each of the deliverables can be used individually and in combination.

Drug shortages are a global issue and the solutions presented here can be used also outside the European Union. The work completed to date should not be regarded as concluding our endeavours; for example, enhancements and further deliverables, including training materials as appropriate, will be developed and made available through the individual organisations. We encourage companies and Health Authorities to implement the solutions summarised in this report and described in detail in the publications from the individual associations/organisations.

2. Recommendations

The industry drug shortages inter-associations team has the following recommendations:

2.1. Industry Communication Principles to Authorities (Communication Level) by EFPIA, EGA, AESGP and PPTA

There is an opportunity to create transparency and predictability in the management of drug shortages by

1. Harmonising the definition of a meaningful disruption to supply
2. Harmonising reporting content with initial categorisation based on PDA's risk triage model
3. Harmonising time point and recipient of the information at National Competent Authorities (NCAs) and EMA

Benefits with a single, harmonised template for reporting are:

- Harmonised notification process across Europe
- Right first time for industry
 - Providing correct and consistent information when a supply disruption can be foreseen
- Faster coordination between NCAs and EMANotified root causes can be trended
 - To provide information / enabling knowledge for management of continual improvements
- Industry trends can be input to prioritisation at inspections
 - When root cause data is generated they will serve as a tool

We conclude that further dialogue and support from Authorities is needed to put this proposal into practice.

2.2. Root Cause Based Prevention (System Level) by ISPE

The *ISPE Drug Shortages Prevention Plan (DSPP)* has identified the need for companies to increase capability in several key technical areas. ISPE's future vision is to facilitate industry's overall ability to continually improve, enabling higher capability, higher quality performance and the establishment of robust and resilient supply chains, thereby facilitating a reliable supply of medicines to patients. The six dimensions of the ISPE *DSPP* provide a structure for how companies, and regulators, may consider their plans for ensuring supply and preventing drug shortages. It is important to realise this is a systematic approach focused on end-to-end supply chain control and capability. This holistic approach facilitates the addressing of a variety of circumstances that may occur, possibly at short notice. Going forward, ISPE will continue to act as global facilitators and integrators in the effort to prevent shortages provoked by manufacturing or quality issues through ongoing projects with other associations; holding forums with industry leaders and regulators; and helping companies build capability through the development of guidance documents, training and education programmes. We recommend the ISPE *DSPP* to both industry and regulators and warmly invite you to join with us as we seek to better serve patients all around the world.

Some of the key recommendations are summarised below. More details are found in the *DSPP*.

- Corporate Quality Culture and a Robust Quality System: A corporate quality culture and a robust quality system are foundational to each other. In relation to mitigating shortages and ensuring patient supply, companies should assess their quality culture against the *DSPP* recommendations and ensure it supports a robust quality system which embraces a holistic lifecycle approach to product quality.

- Metrics: companies should select metrics as indicators of an effective quality system and potential shortage vulnerability: these metrics should follow principles of continual improvement.
- Business Continuity Planning: a prospective risk management process should be undertaken to ensure a robust and resilient supply chain.
- Communications with Authorities: companies should establish clear processes for conducting rapid and clear communications with the various regulatory agencies around the globe to ensure a consistent and transparent message between the company and its regulators and, if there is a shortage, to reduce the amount of manufacturing downtime needed to get the site compliant and back up and running.
- Building Capability: Companies should ensure capability (i.e., the appropriate collective skills, abilities, and expertise of an organisation) across all elements of the drug shortage prevention plan.

2.3. Risk Based Prevention (Product Level) by PDA

PDA recommends that companies establish robust plans at a product level, where deemed necessary, to proactively prevent and manage potential drug shortages caused by manufacturing and quality issues. To support this recommendation, PDA's Technical Report on "A Risk-Based Approach for Prevention and Management of Drug Shortages" provides the following:

- A holistic risk-based framework at a product level for prevention and management of drug shortages caused by manufacturing and quality issues.
- A risk triage model that can be used to assess drug shortage risks and implement appropriate controls in the end-to-end value chain for manufacturing and distribution of a product.
- Templates for developing a Drug Shortage Risk Register and a Drug Shortage Prevention and Response Plan. These templates can be used directly by companies to enable proactive identification of potential drug shortage risks, and establish mitigation activities.
- A framework that companies can use to engage in proactive dialogue with health authorities to expedite certain post-approval changes described in the Technical Report (TR) for products at risk of drug shortage. PDA is currently developing general global change protocols (gCP) for specified post-approval changes to facilitate consistency and a standardised approach.

Going forward as follow-on to its technical report on drug shortages, PDA will continue to work on additional practical, specific, and directly applicable solutions to the drug shortage problem based on its combined membership's strong technical, science, and quality background and experience. This includes continued work on developing specified global change protocols, establishing and leading training on the TR, the risk triage tool and templates, and leading further discussions with industry and health authorities. PDA will continue their discussions on innovative and implementable solutions to the drug shortage problem through complementary coordination with other associations.

3. Summary of Work Stream Deliverables

In this section we summarise the content of the deliverables from the three work streams.

3.1. Industry Communication Principles to Authorities (Communication level) by EFPIA, EGA, AESGP and PPTA

By law, Marketing Authorisation Holders have to notify Competent Authorities about medicines supply disruptions related to quality and manufacturing issues. Effective communication is one element that can contribute to the overall prevention and management of medicines shortages. However, such effective communication is compromised at the moment by the diversity in expectations and data requirements across Medicines Agencies in the EEA.

The pharmaceutical industry therefore proposes a framework for improving the communication that includes:

- An identical trigger point for notification based on:
 - Agreed definition of a meaningful disruption to supply, and
 - Triage process that evaluates the risk associated with a potential supply disruption;
- A harmonised reporting content;
- An agreed single time point and recipient of the information for all nationally and centrally approved products.

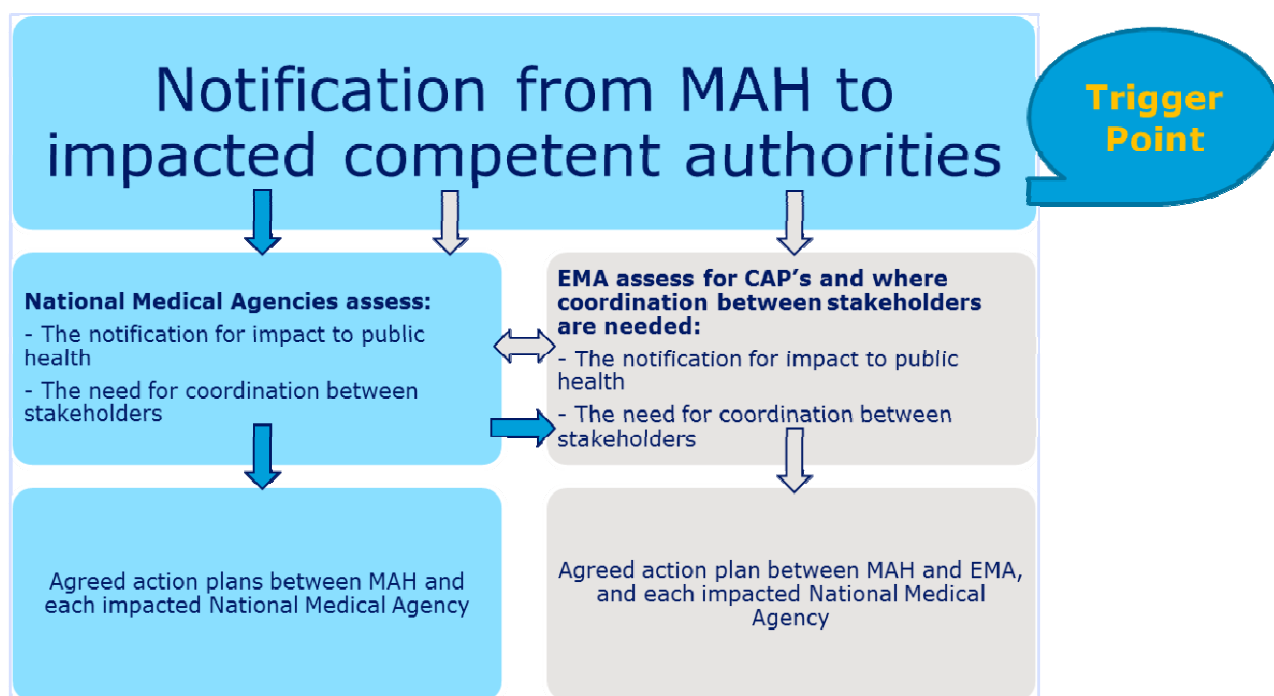


Figure 1: Notification from the Marketing Authorisation Holder (MAH) to impacted Competent Authorities

Industry recognises that building such a framework requires collaboration by the stakeholders and looks forward to discussing the proposals in this paper with Competent Authorities.

How can the communication principles be used, what are the benefits?

Regulators: An opportunity for transparency, predictability and use of a risk-based approach

- Further dialogue with industry on how to get consistent notifications, including easy access to a simple uniform template posted on agencies' webpages.
- Benefits of a single, uniform template:
 - Harmonised notification process across Europe
 - Predictability & Transparency – Right first time for industry / providing correct and consistent information when a supply disruption can be foreseen
 - Faster coordination between National Competent Authorities and EMA
 - Notified root causes can be trended to provide information / enabling knowledge for management of continuous improvement

Inspectors: An opportunity to facilitate continual improvement

- Initially support creation of transparency, predictability and use of a risk-based approach, hereafter:
- Benefits:
 - When root cause data is generated and trended they will be a tool for input to prioritisations of topics discussed at inspections

Industry: Bring awareness

- Notifications delivered timely to Competent Authorities
- Further dialogue with Competent Authorities to establish a simple uniform template to be used across Europe
- Benefits:
 - Predictability & Transparency
 - Right first time and faster information to Competent Authorities when a supply disruption can be foreseen

Industry supports the collaborative efforts to address medicines shortages.



Figure 2: Landscape of Information and Communication Paths by Manufacturers

The EMA initiative and collaborative associations work constitute one piece of the medicines shortages. The complexities associated with medicines shortages (causes, products, markets, timing etc.) necessitate an integrated solution involving all stakeholders and extending beyond quality and manufacturing factors.

3.2. Root Cause Based Prevention (System Level) by ISPE

The *ISPE Drug Shortages Prevention Plan (DSPP)* is an internationally relevant plan of value to all sectors of industry and its regulating authorities. The plan builds upon data from ISPE's 2013 Drug Shortages Survey, which provided clear evidence that mitigating shortages requires a holistic approach that encompasses both the organisational and technical issues affecting drug manufacturing and quality. The Drug Shortages Survey also highlighted the need for industry to conduct an appropriate examination of the underlying technical, scientific, manufacturing, quality, and compliance issues associated with a company's supply chain as it relates to its ability to source, manufacture, and distribute products.

The ISPE Drug Shortages Task Team defined the following "building blocks" for a sustainable drug shortages prevention plan:

- Corporate Quality Culture
- Robust Quality System
- Metrics (specific to drug shortages)
- Building Capability – for example, organisational and personal competencies
- Business Continuity Planning – for example, crisis management
- Communication with Authorities

The ISPE *DSPP* uses this model to serve as a "roadmap" to assist both the pharmaceutical industry and regulators in identifying, managing, resolving and preventing constraints in manufacturing operations which may result in abnormal restriction in supply. The Plan also addresses optimal organisational strategies, effective manufacturing and integrated quality systems, and appropriate measures of supply chain robustness.



Figure 3: ISPE Drug Shortages Prevention Plan (DSPP)

How can the ISPE *DSPP* be used, what are the benefits?

Regulators:

Much of the plan focuses upon better implementation of a site's (or company) quality system -and it is the GMP aspects of quality systems that are inspectable. Where supply interruptions occur or threaten, inspectors should find this plan a valuable resource not only in regard to these minimum standards, but in assisting industry towards more general quality improvement efforts.

Industry:

After reviewing the ISPE *DSPP* the reader should better understand the regulatory expectations regarding interruptions to drug supplies caused by manufacturing or quality issues and their potential to result in drug shortages; key elements from the ISPE Drug Shortages Survey; and specific building blocks to help industry and health authorities collaborate on reducing drug shortages globally. However, it is important to recognise that the Plan is not intended to be read from cover to cover or indeed in any particular order. The plan will be most useful if considered a reflection paper against which all manufacturers, including Contract Manufacturing Organisations, can compare their entire supply chain and challenge their current processes, systems and practices in order to identify gaps and opportunities for improvement. Secondly, the Plan is a tool kit from which individual tools may be selected as appropriate. While it is essential to recognise the inter-relationships of the six dimensions, many readers will find that one or two dimensions provide the greatest insight and value, especially when considering the discussion points and industry examples.

3.3. Risk Based Prevention (Product Level) by PDA

PDA's Technical report "Risk-Based Approach for Prevention and Management of Drug Shortages" is an easy step-by-step guide to proactively identify and manage drug shortage risks caused by manufacturing and quality issues in the end-to-end product value chain.

The PDA technical report provides a practical approach consisting of

1. A holistic risk-based framework at a product level for prevention and management of drug shortages caused by manufacturing and quality issues.
2. A risk triage model that can be used to assess drug shortage risks and implement appropriate controls in the end-to-end value chain for manufacturing and distribution of a product.
3. Templates for developing a **Drug Shortage Risk Register** and a **Drug Shortage Prevention and Response Plan** at a product level especially for products at risk level A (based on their therapeutic use and the availability of alternative treatments).

The framework provided in the report also supports and enables Marketing Authorisation Holders (MAHs) to meet the requirements of Section 506C of the Federal Food, Drug and Cosmetic Act and Article 13 of the EU GMP Directive 2003/94/EC, to notify relevant health authorities in a timely manner in the event of a meaningful disruption or potential drug shortage.

The technical report also describes management responsibilities and expectations related to prevention, management and notification of drug shortages to health authorities. It also provides ways for the industry to engage more proactively with health authorities through use of post-approval change management plans and harmonised global change protocols, to expedite the review and approval of post-approval changes by multiple health authorities. Such protocols may be helpful for companies to address the risk of drug shortages due to aging facilities, processes, and analytical technologies by modernising their facilities and implementing new technologies (equipment, processes, and analytics). The report leverages the guidance developed by EFPIA, EGA, AESGP, and PPTA for communications between MAHs and health authorities.

As the risk to patients from a potential drug shortage increases, the level of rigor, effort, and cross-functional collaboration within an organisation to address the risk should also increase. This effort should be coupled with effective and timely communication between the MAH and health authorities to proactively manage drug shortage risks.

Development of PDA's risk-based approach for prevention and management of drug shortages started in 2012 as part of the Paradigm Change in Manufacturing Operations (PCMO[®]) project. An overview of the approach was published in April 2014 in a PDA Letter article, and is elaborated in detail in the technical report.

How can the PDAs Risk Based Prevention TR be used, what are the benefits?

Regulators (including inspectors): The TR can be used by regulators to enable the following:

- A shift from reactive to proactive management of drug shortage risks in alignment with the principles of ICH Q9, *Quality Risk Management* and ICH Q10, *Pharmaceutical Quality System*
- Ensure that the QRM policy and procedures at companies include proactive management of product availability (drug shortage) risks
- Raise awareness and reinforce application of the risk-based concepts, tools & templates in the TR at a product level
- Bring attention to the training resources for companies that are in more of a reactive state related to management of shortage risks

- Leverage relevant elements of the Drug Shortage Risk Register (especially for medically necessary, life-saving or life-supporting products) to engage in proactive dialogue and partnership with companies on management of drug shortage risks

Industry:

Practical application of the risk based framework at a product level including the risk triage tool and templates.

Companies are advised to have robust QRM and knowledge management systems to both prevent (proactive) and respond (reactive) to drug shortages. Proactive risk management of drug shortages should involve the following:

- Categorising each product by criticality based on its indication and patient needs
- Establishing a **Drug Shortage Risk Register** (single source of information on risks that can result in drug shortages) by proactively identifying and assessing risks (to quality, compliance, and supply) that could lead to a shortage
- Ensuring timely reduction and management of risks by completing risk control actions defined in the risk control plan, based on criticality.
- Establishing a **Drug Shortage Prevention and Response Plan**, with a particular focus on medically necessary, life supporting or life sustaining products. Communication of plans with Health Authorities.

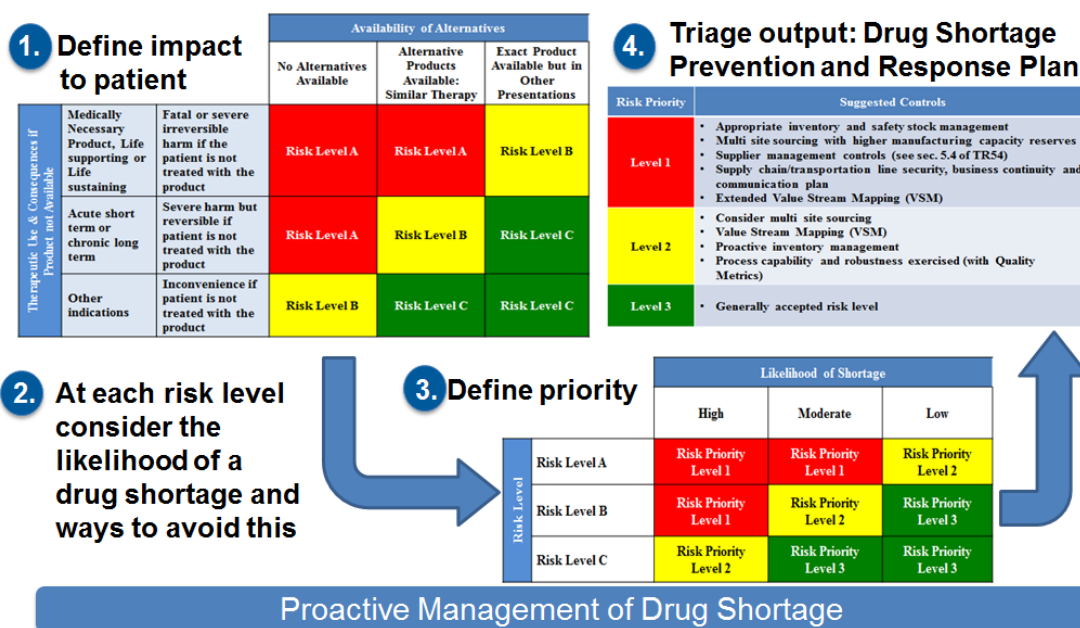


Figure 4: A Triage: Categorisation, Patient impact and End-to-end Controls

The steps in the triage process depicted in Figure 5 are as follows:

1. Identify risk level (impact to patient) based on therapeutic use and availability of alternatives
2. Determine the likelihood of a drug shortage for the product
3. Determine the risk priority level based on a combination of impact to patient and likelihood of a drug shortage for the product
4. Based on the risk priority level, plan and implement the suggested risk controls for the assessed product.

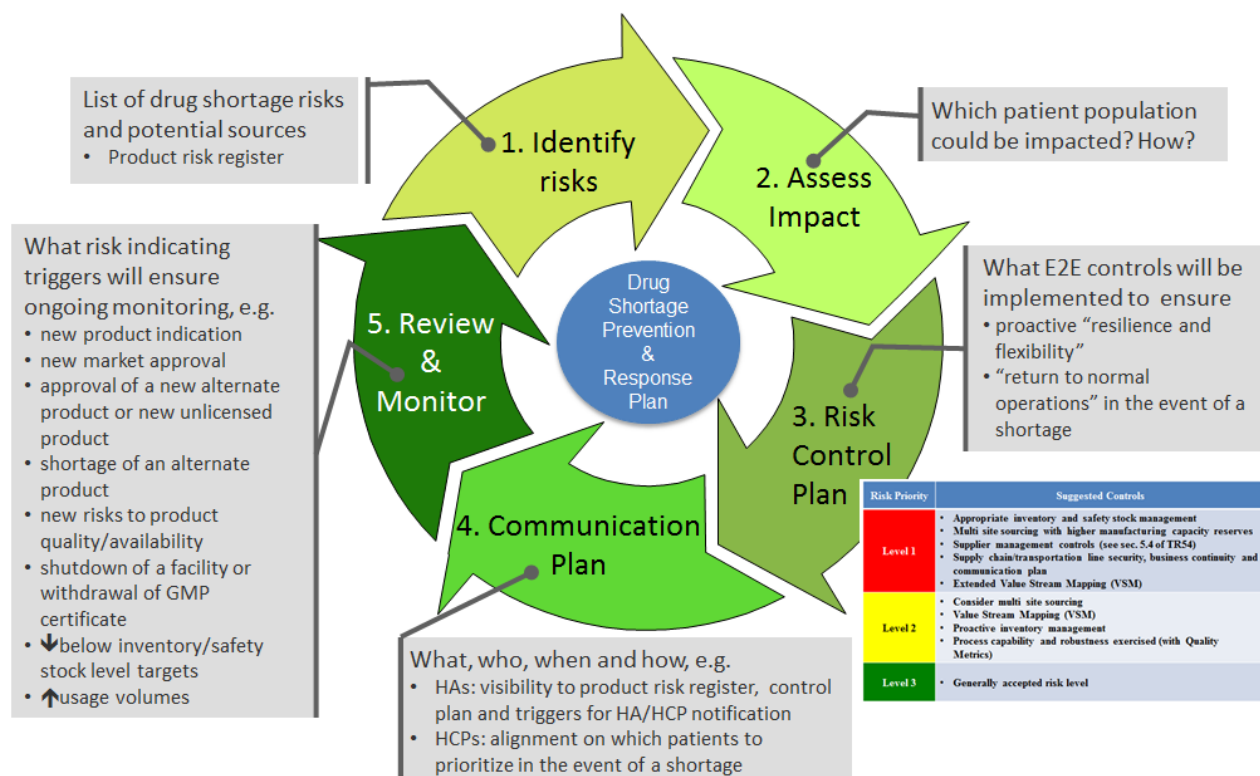


Figure 5: Drug Shortage Prevention & Response Plan for a Product

Each of these steps is described in detail in the Technical report and templates are provided.

4. Deliverables for Practical Implementation

The European Medicines Agency (EMA) summarises the overall framework on drug shortage

- This page contains information related to medicine shortages and how they are reported and assessed by the European Medicines Agency (EMA):

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000588.jsp&mid=WC0b01ac05807477a5

The following documents have been developed by the inter associations team

- Quality and manufacturing driven supply disruptions: industry communication principles to Authorities (EFPIA / EGA / AESGP / PPTA), 2014; <http://efpia.eu>, www.egagenerics.com, <http://www.aesgp.eu>, <http://www.pptaglobal.org>.
- ISPE Drug Shortages Prevention Plan (DSPP), 2014; <http://www.ispe.org/drug-shortages-initiative>.
- Risk-Based Approach for Prevention and Management of Drug Shortage, PDA Technical Report No. 68, 2014; www.pda.org/DrugShortage.

5. Acknowledgement

The associations represented here thank the EMA for the opportunity to contribute to this important public health issue. The task force has welcomed input from the EMA and the national competent authorities e.g. of the UK, Belgium, Ireland, France, and Spain. We collectively commit to continue working together to best serve the industry, its regulators and the patient through the complementary nature of our joint efforts.

6. About the Drug Shortage Inter-Associations Team and Contacts

Each of the associations on this team has ongoing activities to address the topic of drug shortages. They brought their own uniqueness to this joint team based on membership, strategic plan, and focus. This team was established to collaboratively build on these unique perspectives to address the overall topic of preventing drug shortages caused by manufacturing and quality issues. The organisations focused on the scientific and technical elements of restrictions in supply due to quality and manufacturing issues including root causes, risk, prevention, and control throughout the supply chain in the responsibility of a manufacturer / Marketing Authorisation Holder. It should be noted that economic and business related root causes as well as supply interruptions by other players in the supply chain were out of scope of this team's deliverables.

Table 1: For more details please contact the following representatives for the different associations:

Focus	Association	Contact person	e-mail address
Root-cause based prevention	International Society for Pharmaceutical Engineering (ISPE)	John Berridge, ISPE	johnberridge@btopenworld.com
Risk-based prevention	Parenteral Drug Association (PDA)	Georg Rössling, PDA	roessling@pda.org
Communication	European Federation of Pharmaceutical Industries and associations (EFPIA)	Sylvie Meillerais, EFPIA; Birgitte Holst, NovoNordisk	sylvie.meillerais@efpia.eu ; bho@novonordisk.com
	European Generic Medicines Association (EGA)	Julie Maréchal-Jamil, EGA	jmarechal@egagenerics.com
	Association of the European Self-Medication Industry (AESGP)	Christelle Anquez-Traxler, AESGP	C.Anquez@aesgp.eu
	Plasma Protein Therapeutics Association (PPTA)	John Delacourt, PPTA	jdelacourt@pptaglobal.org