EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Update on Product Shortages Due To Manufacturing/GMP And Quality Issues

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Reminder about Shortages due to quality and manufacturing problems

- In November 2012 EMA published a reflection paper and implementation plan with 2 main objectives;
  - Provide a framework for assessment
  - Raising Awareness and seeking solutions
- EMA team co-ordinated CHMP sub-group and HMA Virtual group

A Framework for assessment

- Developed common understanding of critical medicine/develop decision tree/clarify national input into EU advice/communication (public catalogue)
- Facilitate Benefit / Risk evaluation through template AR (points to consider) and closing AR (retrospective impact of shortage) plus resource guidance.
- Risk indicators for shortages (manufacturing and quality) developed to identify products at risk.
- Crisis situations resulting from product shortages addressed in context of EU Incident Management Plan (IMP)
- Develop international co-operation to foster sharing of information

Product information
Scientific advice and protocol assistance
Scientific guidelines
Innovation Task Force
SME office
Paediatric medicine
Geriatric medicine
Orphan designation
Herbal products
Referral procedures
Article 58 applications
Compassionate use
Pharmacovigilance
Data submission on authorised medicines
Advanced therapies
Clinical trials
Inspections
Falsified medicines
Quality by design
Product defects and recalls
Parallel distribution
Medicine shortages
Shortages catalogue
Antimicrobial resistance
Pandemic influenza
New countries/EFTA
Non-pharmaceutical products
Fees

Overall framework

In the European Union, most medicine shortages are dealt with at national level by the national competent authorities.

However, the EMA can be involved in certain situations, for example when a medicine shortage is linked to a **safety concern** or affects **several Member States**.

Medicine shortages can occur for many reasons, such as **manufacturing difficulties** or problems affecting the **quality of medicines** that can impact on patient care. Regulatory authorities within and outside Europe are increasingly working together to prevent shortages and to limit their impact whenever they occur.

European regulatory authorities aim to minimise the impact of medicine shortages on patients by:

- working with pharmaceutical companies to resolve manufacturing and distribution issues;
- sharing information with international partners about alternative sources of supply;
- seeking input from patients and healthcare professionals on the impact of medicine shortages, to support decision-making;
- taking measures to allow alternative medicines or suppliers to be used.

The Agency maintains a catalogue of shortages that it has assessed.

EU-level coordination

The EMA published a **reflection paper** in November 2012 concerning public health incidents that can arise due to manufacturing disruptions linked to problems such as quality defects or Good-manufacturing-practice (GMP) compliance issues. It concerns human medicines regardless of their route of authorisation, where there is an identified need to coordinate the assessment and any risk-reducing actions at EU level. An **implementation plan** was also drawn up, defining actions to co-ordinate the assessment of shortages, develop risk-minimisation measures, alleviate the impact on patients and communicate within the EU regulatory network:

- Reflection paper on medicinal-product supply shortages caused by manufacturing / good-manufacturing-practice compliance problems
- Reflection paper on medicinal-product supply shortages caused by manufacturing/good-manufacturing-practice compliance problems - Implementation plan 2012-2015

On 14 October 2013, the Agency organised a public workshop on product shortages due to manufacturing and quality problems in order to explore and develop a proactive approach to their prevention.

Based on the implementation plan and input gathered at the workshop, the EMA has developed a set of **documents to support medicines regulators** involved in the EU-level coordination of shortage situations due to GMP non-compliance/quality defects:

- Criteria for classification of critical medicinal products
- Decision tree on escalation from national to European level
- Points to consider for the overall assessment of a supply shortage of a medicinal product due to GMP Non-compliance /quality defects
- Closing report on assessment of a supply shortage of a medicinal product due to manufacturing and quality problems
- Resources for issuing treatment recommendation during shortages of medicinal products
- Risk indicators for Shortages (Manufacturing and Quality)

Public catalogue of shortages

Good-manufacturing-practice and good-distribution-practice compliance
Product defects and recalls

Raising Awareness / Proactive approach

- Raise awareness of the impact of product shortages and stimulate industry reaction and improvement in Business Continuity Planning.
- Promote better and proactive risk management by Marketing Authorisation Holders – resilience in supply chains.
- Held a workshop with stakeholders

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/10/event_detail_000796.jsp&mid=WC0b01ac058004d5c3

Industry associations have delivered.

A positive response

- Formed an Inter-Association Task Force (unique initiative)
- ISPE – ISPE Drug Shortages Prevention Plan – October 2014
- AESGP/EFPIA/EGA/PPTA – Industry Communication Principles to Authorities – Q4 2014
- PDA – Technical Report on "Risk-Based Approach for Prevention and Management of Drug Shortages“ – Q4 2014

Drug Shortages Prevention Plan– a holistic approach to prevention of shortages due to manufacturing quality problems

Features

- Follows ISPE's shortages survey
- Discussions at every ISPE conference during 2014
- A toolbox and best practice examples to help stakeholders correct and prevent manufacturing quality issues that can create supply disruptions & respond to and manage such disruptions should they occur.

Risk-Based Prevention of Drug Shortage

Foundational concepts

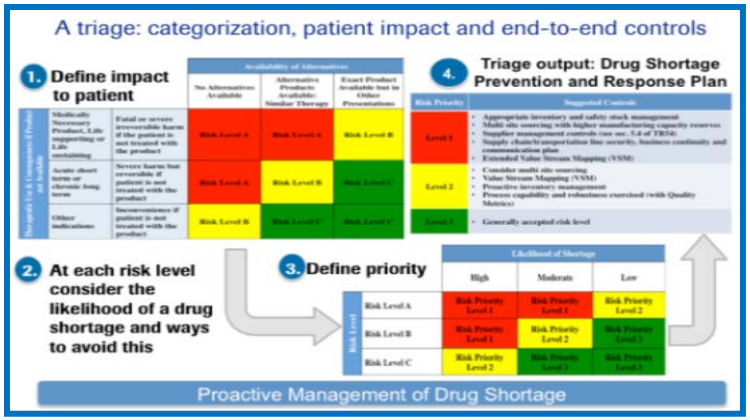
1. **Risk-based triage of products**

   – establish preventive end-to-end controls for drug shortage risks based on criticality of the product, patient impact and overall product risk evaluation.

2. **Establishment of a Product Risk Register and a product Drug Shortage Prevention and Response Plan**

   – A holistic framework and simple templates at product level

1.



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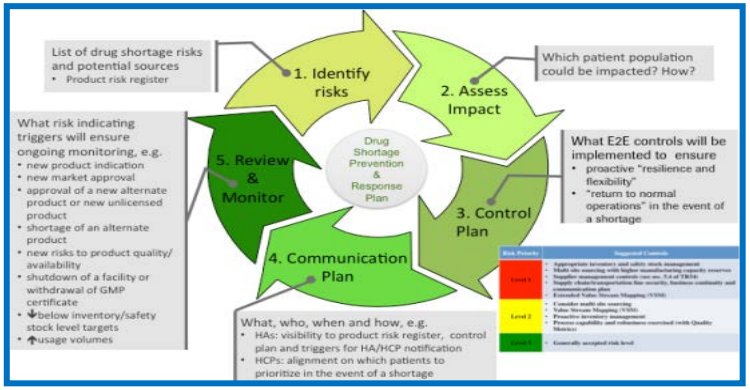
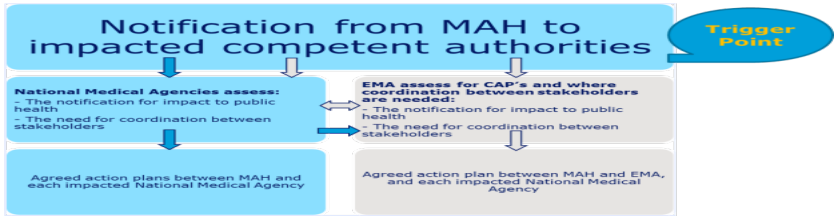


PDA Parenteral Drug Association

Communication Principles

Deliverables

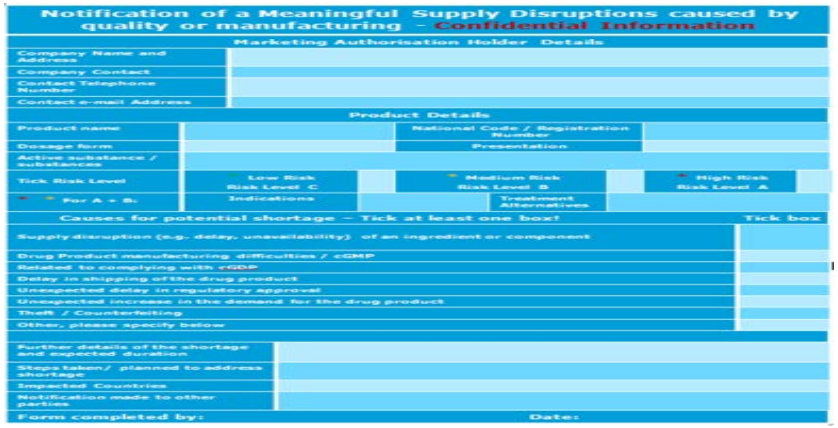
1.Harmonised definition of a meaningful disruption to supply



2.Harmonised reporting template with initial categorisation based on PDAs triaging model

Define Impact to Patient		Availability of Alternatives: No Alternatives Available	Alternative Products Available in the Same Class: Similar Therapy	Exact Product Available but in Different Class or Other Presentations
Therapeutic Use & Consequences if Product not Available: Life supporting or Life sustaining	Fatal or severe irreversible harm if the patient is not treated with the product	Risk Level A	Risk Level A	Risk Level B
Acute short term or chronic long term	Severe harm but reversible if patient is not treated with the product	Risk Level A	Risk Level B	Risk Level C
Other indications	Inconvenience if patient is not treated with the product	Risk Level B	Risk Level C	Risk Level C

3.Harmonised time point and recipient of the information at NCA and EMA



Extended Implementation

Developing a “push/pull” approach with industry.

Stakeholder Workshop – October 9th.

Develop and Implement risk-indicators methodology (pilot).

Workshop

Key themes of prevention and communication.

Will be held @ EMA;

- What have participants done since October 2013?
- What do they plan to do following this workshop?
- What do they need in order to proceed?