Inter-Association Task Force

Presentation to EMA Workshop

Prevention of Drug Shortages
Based on Quality and Manufacturing Issues

9th October 2015

Topics for Today

- Background and history of task force
- Summarise our achievements and deliverables against the original remit
- Share progress and future plans by Associations

Cross-Industry Initiative

Nov 2012

- EMA Reflection Paper
  - Provide a framework for assessment
  - Raise public awareness
- EMA Implementation Plan

Oct 2013

- EMA & Stakeholders Public Workshop
  - Challenge to Industry and Associations to formulate proposals to enhance risk-control measures for preventing supply disruptions caused by Manufacturing / Quality problems
  - And to propose the means to communicate such issues to authorities

Nov 2013

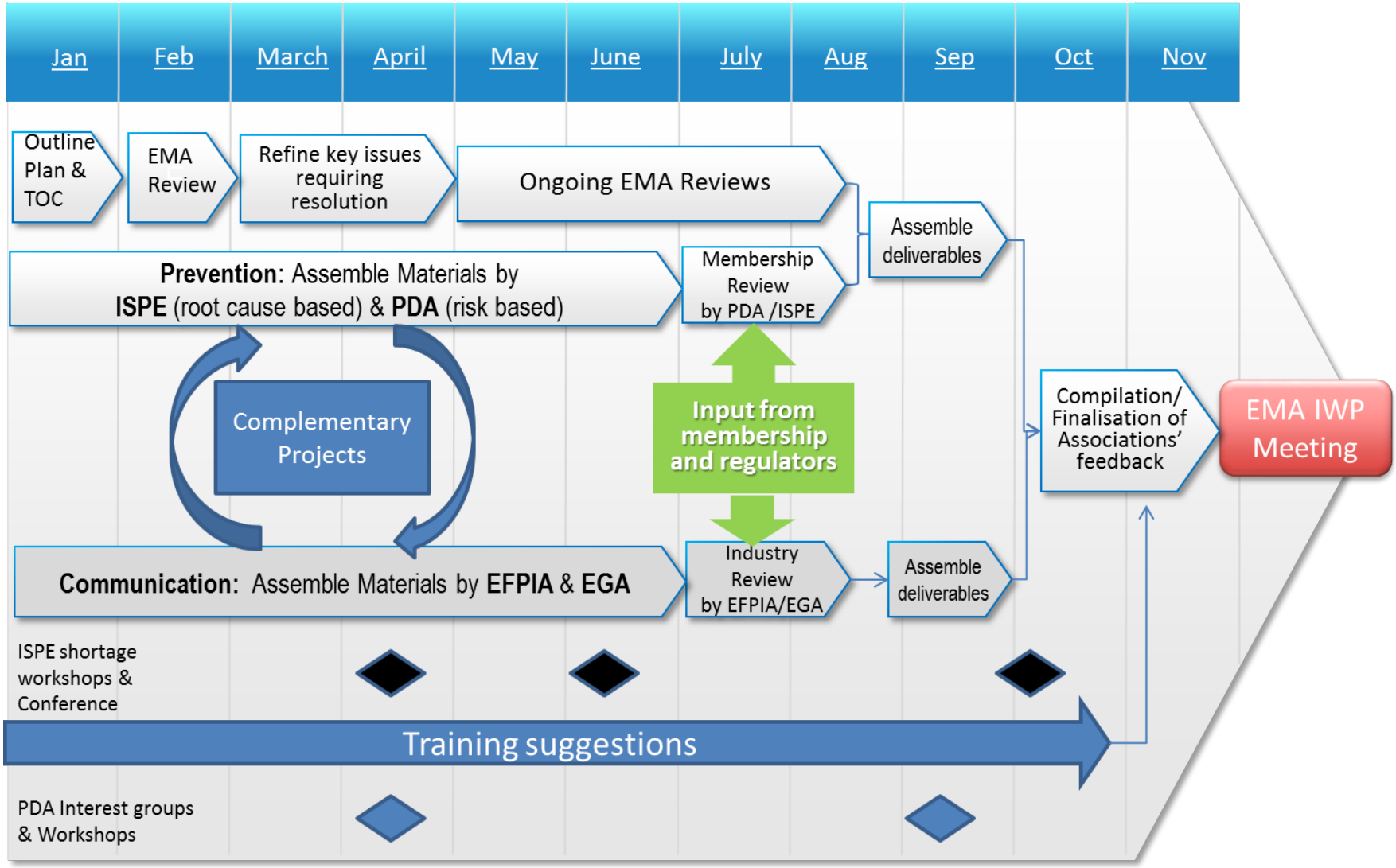
- Inter-association task forces formed
  - ISPE and PDA requested to deliver to the EMA a proposal and plan that addresses the prevention of drug shortages due to manufacturing quality issues
  - EFPIA/EGA/AESGP/PPTA asked to develop a complementary project on communications

Dec 2014

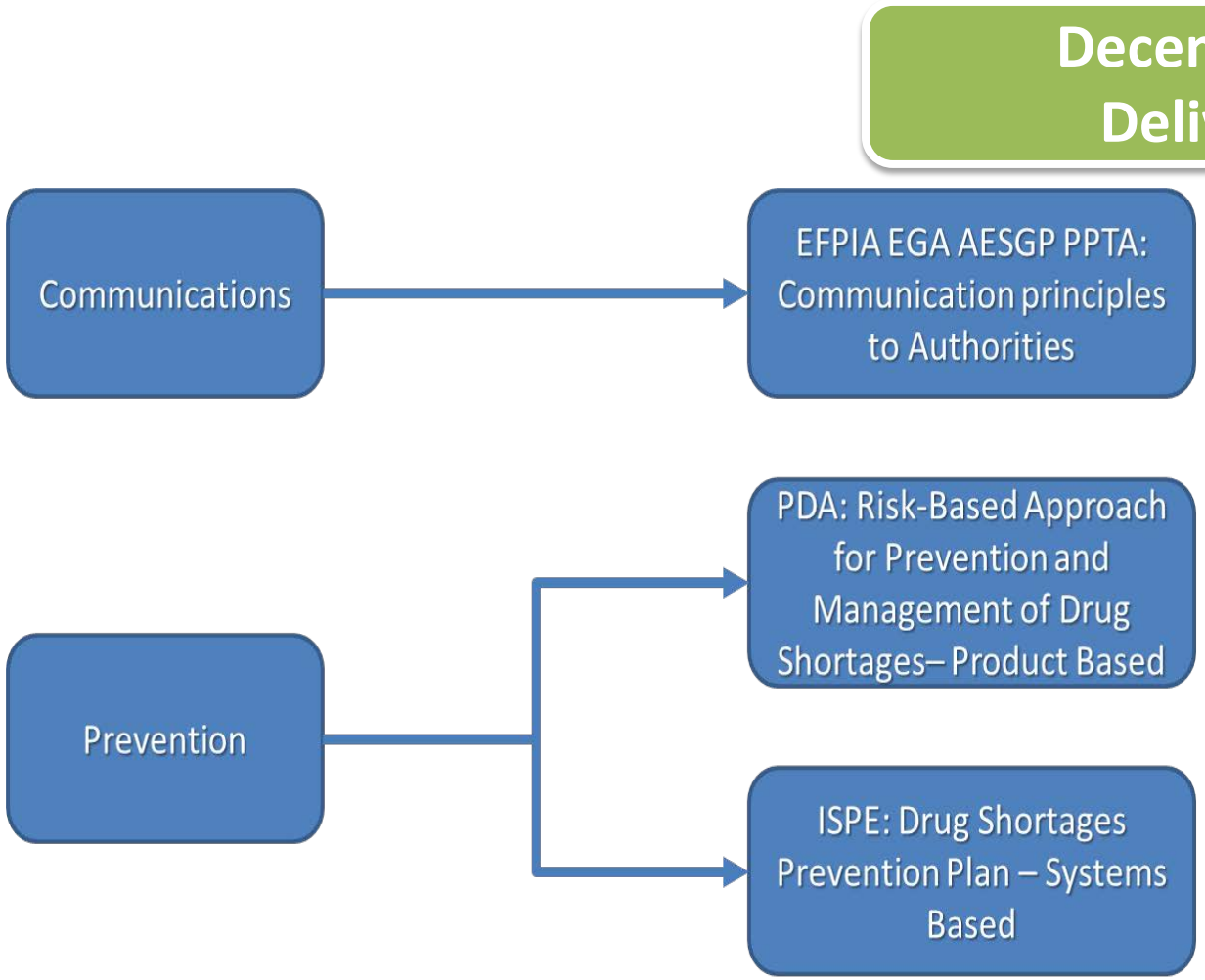
- Presentation to EMA's GMP Inspectors' Working Party

Implementation

2014: from proposals to deliverables



December 2014:
Mission Accomplished and Next Steps



Prevention of Drug Shortages Based on Quality and Manufacturing Issues

Final Report

23. December 2014

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

AESGP efpia EGA ISPE PDA PPTA

2015 - Implementation

- While we are proceeding implementing our deliverables task-force liaison has continued
  - Sharing at conference platforms and presentations
  - Ad-hoc meetings and telecons
- We recognise there is still much to do:-
  - Each Association is now focussed on inculcation in members
    - Training, tools and case studies
  - Collect success stories of implementation of the deliverables

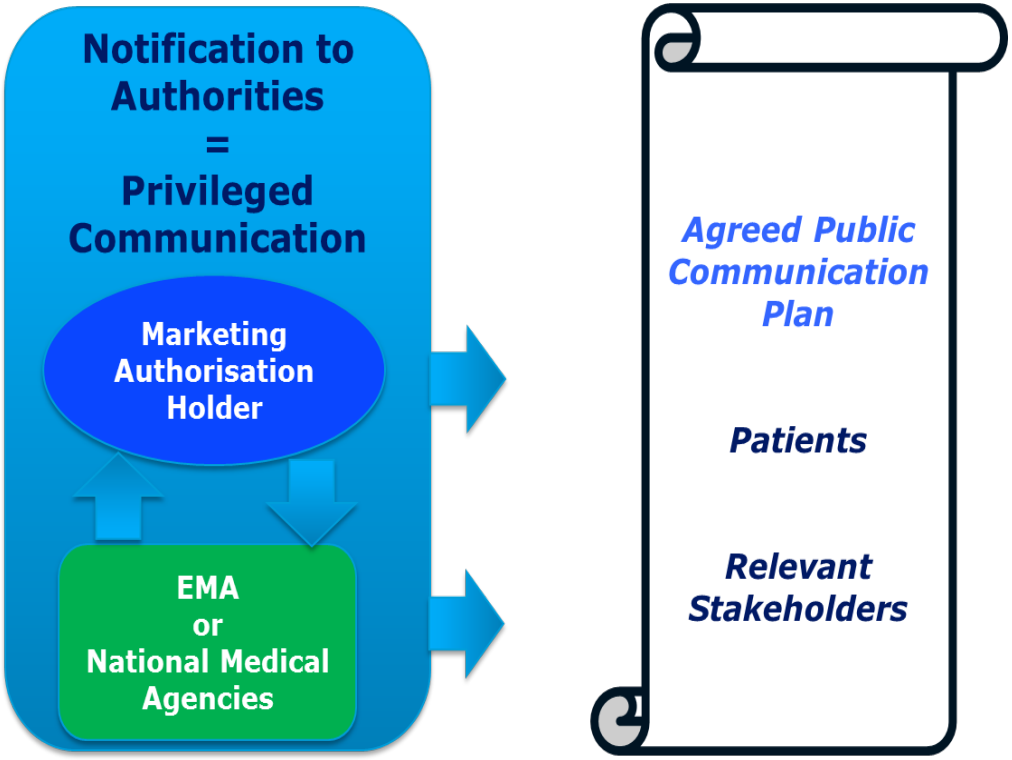
Request to EMA in January 2014.
Baseline metrics on the number of shortages that are due to manufacturing/quality issues so that the value of our activities can be measured.

➢**By mid-2014**

A topic for discussion today


AESGP
efpia
EGA
PPTA

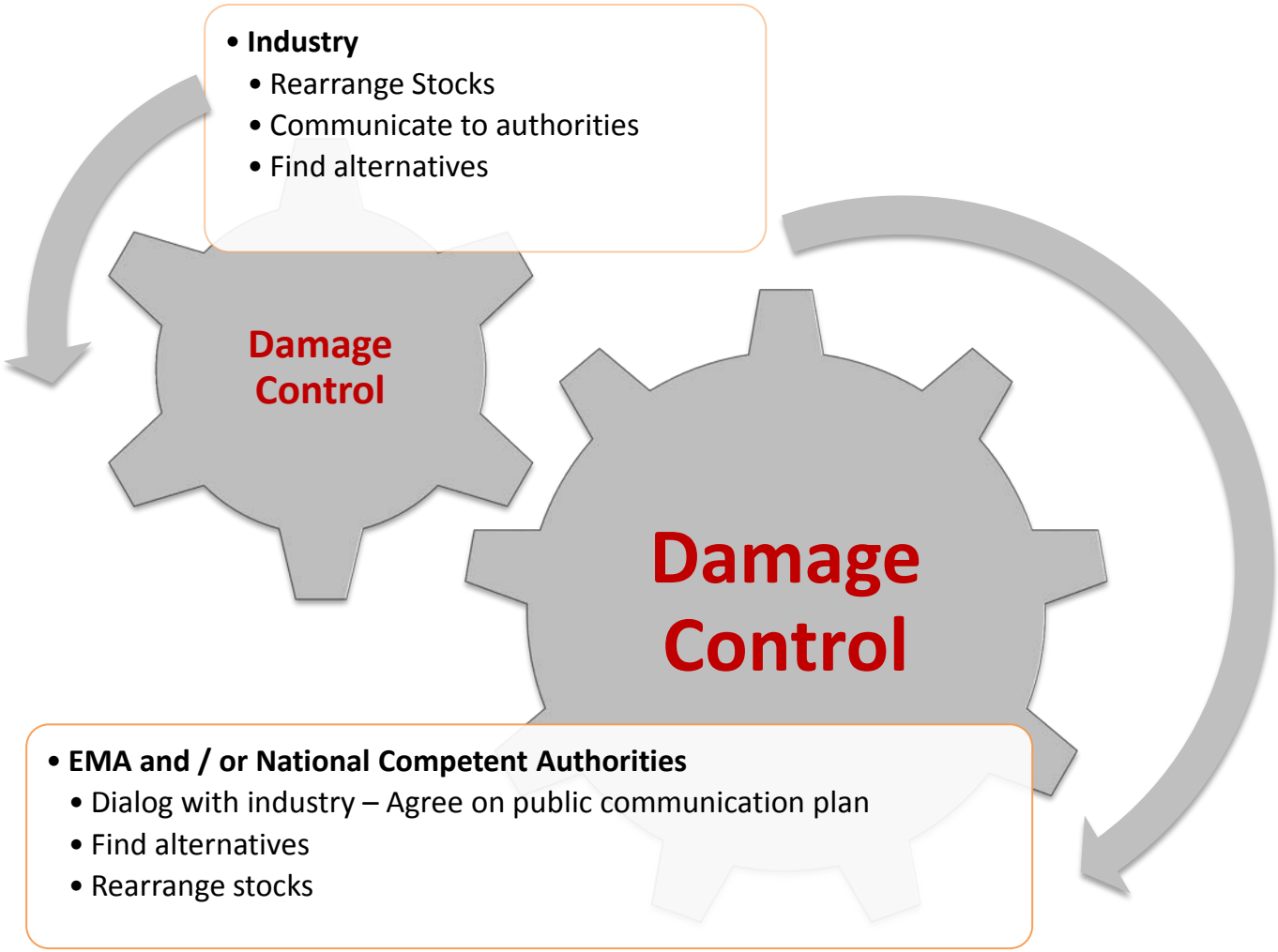
Quality and Manufacturing Driven Supply Disruptions Industry Communication Principles to Authorities



Deliverables

1. Harmonised definition of a meaningful disruption to supply
2. Harmonised reporting content with initial categorisation based on PDAs triage model
3. Harmonised time point and recipient of the information at NCA and EMA

When a disruption of supply emerge!



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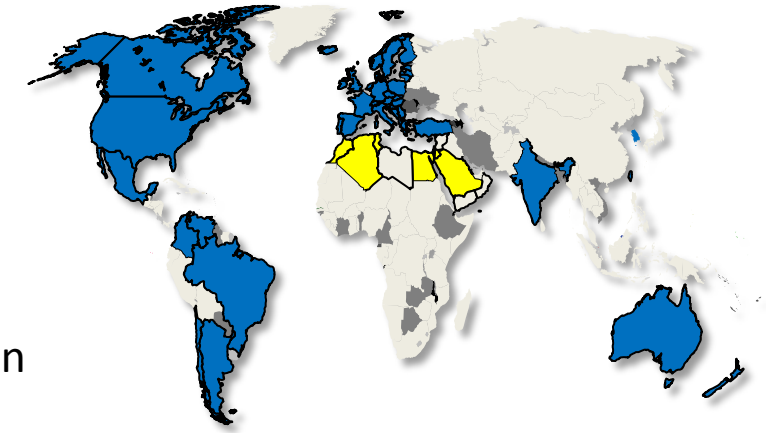
Case Study – from a Global Company with > 1000 products



Global Perspective:
54 Countries Currently Requiring Reporting

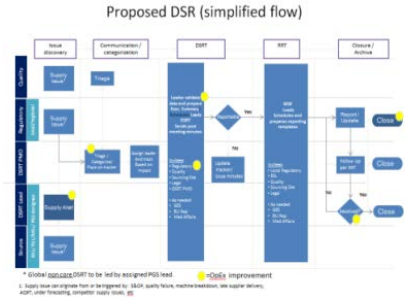
Heterogeneity in Reporting Requirements seen in EU (and beyond)

Reporting details	Various definitions
Which products?	All products, life saving, life supporting, life sustaining, medically necessary, proscribed market list
What to report?	All stock outs, any OOS with patient impact, any stock out > 3 weeks, any OOS w/o alternatives
When to report?	X months in advance, as soon as known prior to stock out, within X days of stock out, not more than X days after stock out, within X days of manufacturing interruption
Who reports?	MAH, wholesaler, manufacturer
How to report?	Email, portal, letter, to third party
How is information held?	Public, private, discretionary
How often to communicate / update?	Every two weeks, as information changes, when asked, not defined

Case Study – from a Global Company with > 1000 products

Responding to the Reporting Challenges

- 2012: Multi-Disciplinary Drug Shortage Reporting Team formed
  - Quality; Regulatory; Supply Chain
  - Process flow mapping
- 2013: Formalised procedures: Corporate SOPs
- 2014: Operational Excellence initiatives including:
  - Voice of Customer exercises
  - IT tools implemented
- 2015: Corporate Audit
  - Governance strengthened
  - Process improvements



New National Regulations creates disharmony in EU e.g.

Moving towards 100 % rapid alert reporting

Noise can take focus from critical medicine

Data from 4-2014 to 1-2015:

36% of Supply Alerts went to Reporting Evaluation step

83% of the Reporting Evaluations became notifications of potential or actual Drug Shortages

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What matters when communicating?

FAST

Clear and Standardised Information in Europe

Every country in Europe have their own way

SLOW

CONTROL OF PRODUCTS

Targeted Information

Open Information

HOARDING OF PRODUCTS

AESGP efpia EGA PPTA

Simplification in EU will Benefits Public Health

An opportunity to create transparency & predictability

- Benefits with a single, harmonised template:
  - 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 National Competent Authorities and EMA
  - Notified root causes can be trended
    - To provide information / enabling knowledge for management of continuous improvements
  - Industry trends can be input to prioritisation at inspections
    - When root cause data trends are generated they will be a tool

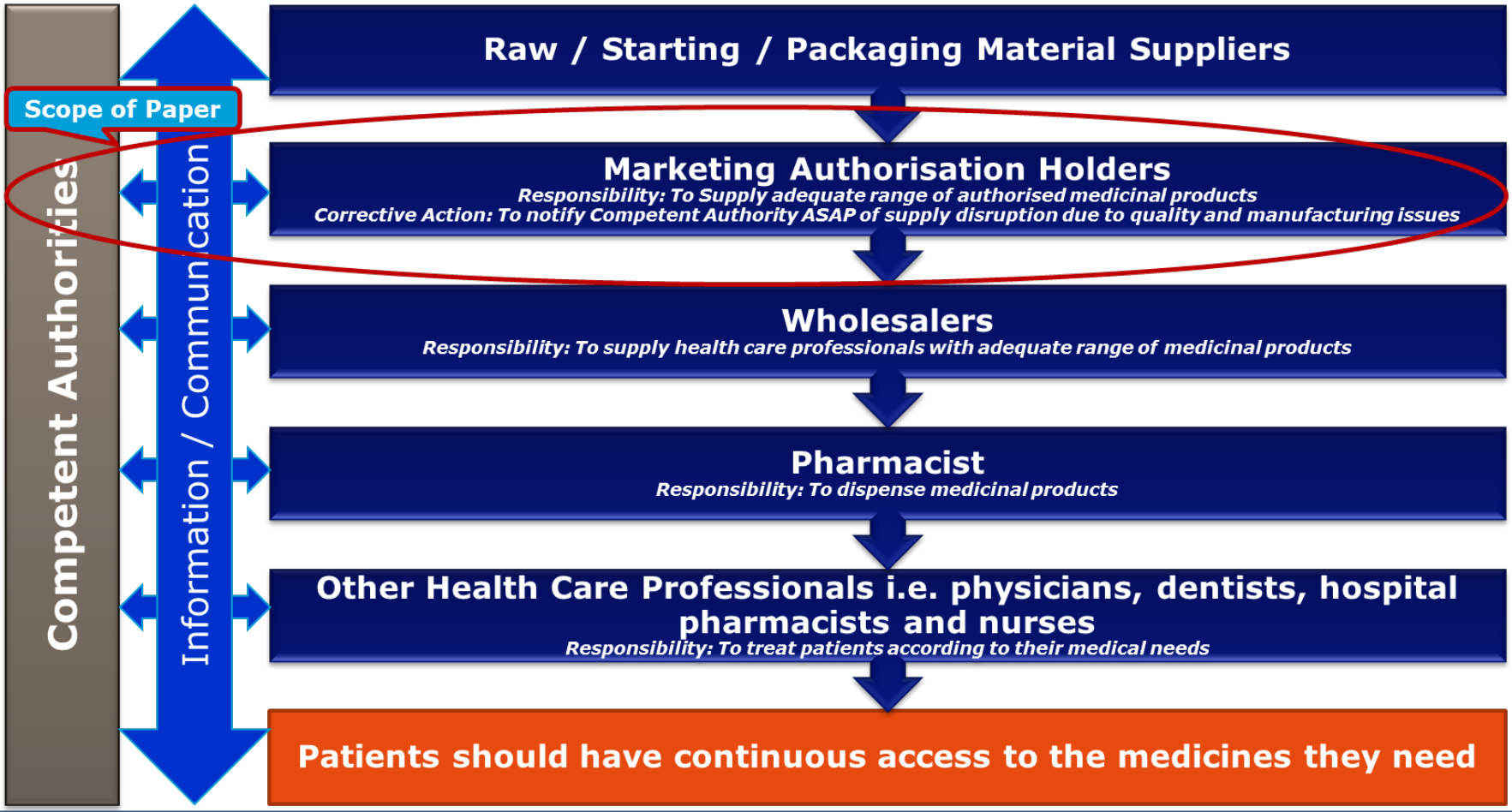
Where are we today

- National Trade Organisations contacted for
  - Raising awareness locally
    - Improvements to avoid supply disruptions
    - Strengthening of reporting processes

  - Contact to NCAs for initiation of harmonisation
- Pending response from EMA and NCAs

Next Steps

Integrated solution with other actors in the supply chain and issue which extends beyond quality and manufacturing factors



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Summary

Europe needs a harmonised reporting process to:

- Improve speed and consistency of reporting
- Facilitate collaboration between industry, EMA, Competent Authorities and other stakeholders to mitigate shortages
- Enable root cause trending to measure improvements and the effectiveness of actions taken

Protecting Patients – Preventing Shortages

Tools and Training

EMA Workshop: 9th October 2015

Fran Zipp

Connecting a World of Pharmaceutical Knowledge

ISPE

ISPE's Drug Shortages Initiative Phase 3:

Awareness, Action, Advancement:

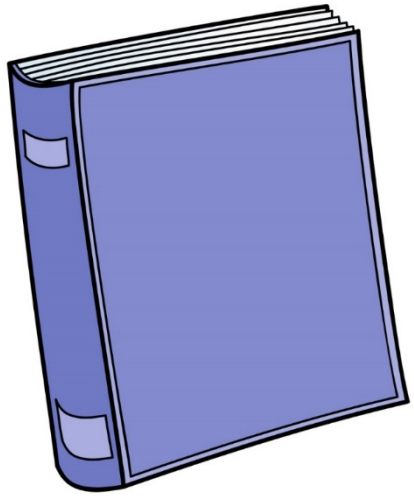
ISPE's *Drug Shortage Assessment and Prevention Tool*

How we are

- Supporting patients
- Assisting Members and their companies
- Reducing shortages

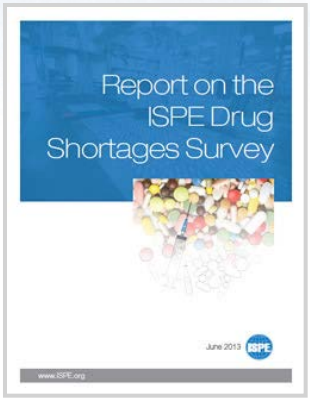
with

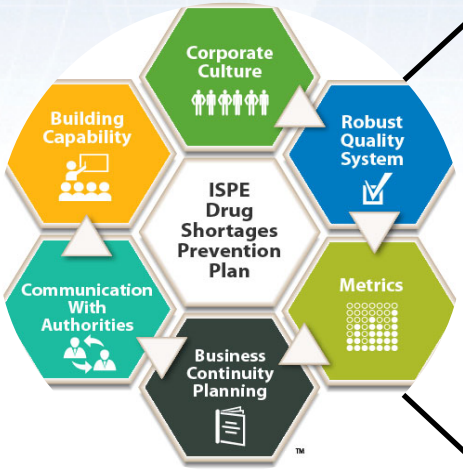
Preparedness Assessment, Gap Analysis and Remediation best practices



Connecting a World of Pharmaceutical Knowledge

2015: Help the Industry Ensure Continuous Availability of Supplies





Awareness

- Leverage Affiliates & Chapters for local language & regulator awareness
- Global and local workshops, training & conferences
- 3rd party collaborations

Action

- Continuing support to EMA and Association initiatives
- Industry and Regulator training
- Action on DSPP recommendations
- **Assisting Industry with gap analysis**

Advancement

- Linkage to Metrics
- New association partnerships
- Global regulatory liaison

Phase I Phase II Phase III

Connecting a World of Pharmaceutical Knowledge

ISPE's *NEW* Tool Supports 5 Steps to Preparedness and Prevention

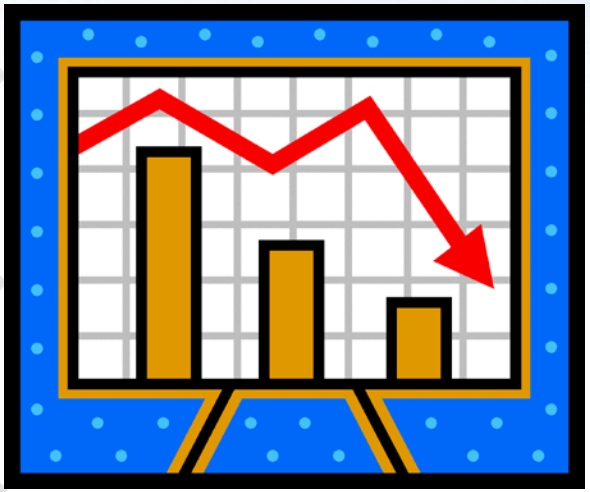
Corporate Commitment
- Identify root causes
- Shortages survey
- DSPP

Gap Assessment
- New tool with gap assessment tools
- Addresses systems, product and communications processes

Remediation
- Webinars
- Case studies
- Training courses

Embed in Corporate Culture
- Metrics
- Maturity assessment for continual improvement included in guide

Engage with Stakeholders
- Dialogue with regulators
- Dialogue with supply chain partners



Connecting a World of Pharmaceutical Knowledge

ISPE

The ISPE *Drug Shortage Assessment and Prevention Tool*

Enables a company (or a regulator) to assess their preparedness for preventing or managing a supply disruption across the six dimensions AND for the product portfolio

Is product availability at risk?

Gap Assessment

Current State

Maturity Assessment

Desired State
As defined by contributions and case studies from members (Industry and Regulators) globally

For Each of the 6 Dimensions

How far are you from the desired state?

Capability Building

Desired State	Maturity Level (1-5)	References to supporting documentation	Comments
Drug Shortage Prevention Control framework			
Is a shortage prevention control framework in place for each product in the supply chain?			
A well-developed definition of potential drug shortage within the organisation and everyone in the entire supply chain is aware of this definition.			

Next Steps

- ISPE's membership world-wide remains committed to support patients through the reliable supply of high quality medicines.

- The ISPE *Drug Shortage Assessment and Prevention Tool* is a first - a unique contribution to the prevention of medicine shortages.
  - Assists all stakeholders to assess their corporate systems and product risks and embark upon remediation and continual improvement.
  - It is addresses shortages on a global basis in a way that is universally applicable - as all sites use a quality system.
  - It provides a mechanistic understanding between root cause and shortages
  - Will be launched on November 9th and made freely available to all ISPE members.

- Complemented by comprehensive and wide-ranging offering of training that will support corporations, senior managers and production team leaders, and all those who regulate the production of medicines.

Connecting a World of Pharmaceutical Knowledge

Awareness

- The ISPE *Drug Shortage Assessment and Prevention Tool* will be promoted in all ISPE affiliates & conferences
- Implementation is a proven strength for ISPE members:
  - 2 or 3 telecons every week with some 50 members engaged
  - Conference sessions, as well as collaborations with other groups in Europe and the USA are planned

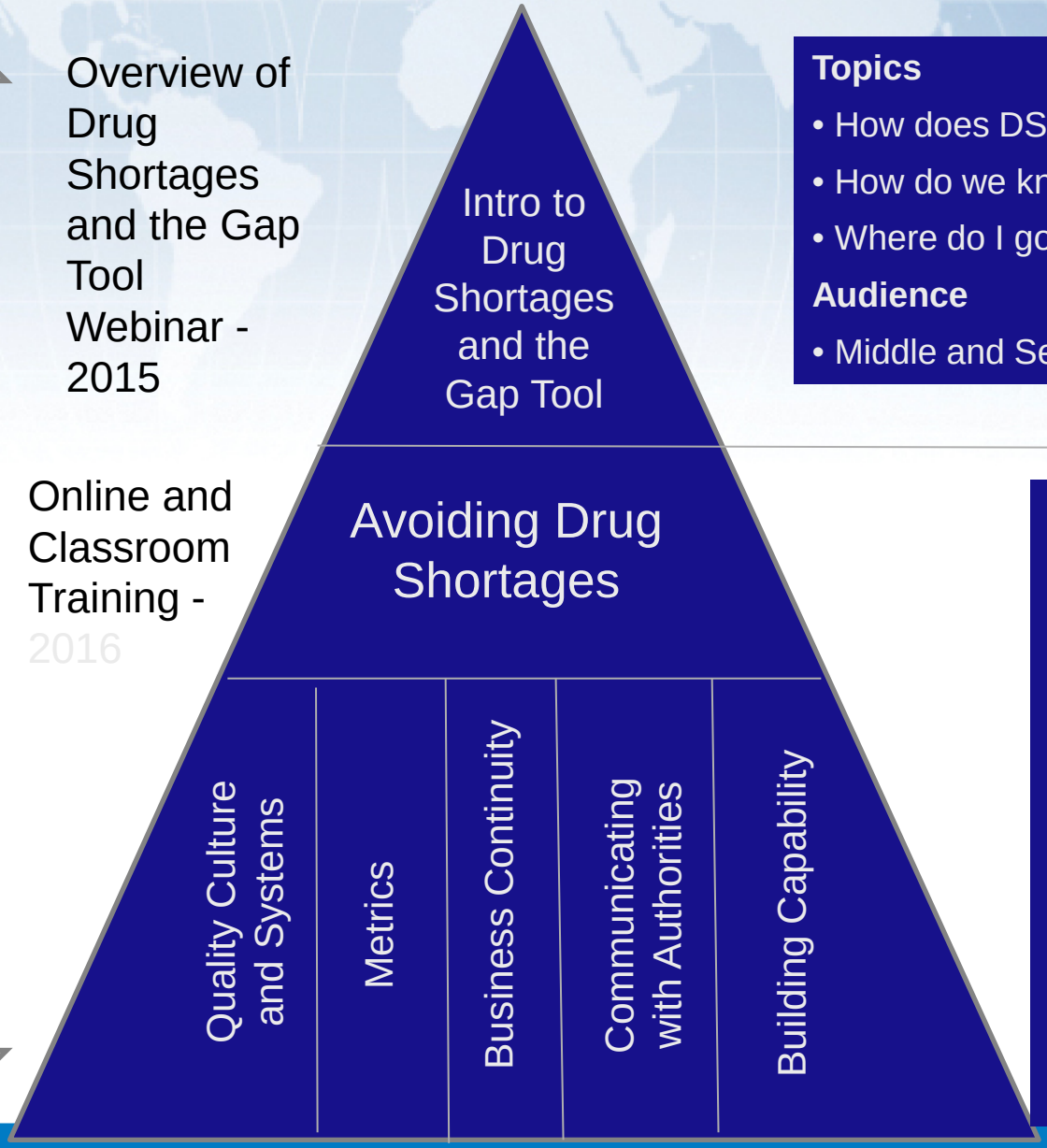
Connecting a World of Pharmaceutical Knowledge

ISPE Drug Shortages Knowledge Products

Action

Overview of Drug Shortages and the Gap Tool Webinar - 2015

Online and Classroom Training - 2016



Topics

- How does DS impact my organisation?
- How do we know we have a problem?
- Where do I go for more detail?

Audience

- Middle and Senior Management

Topics

- How does DS impact my organisation?
- Root causes of DS?
- How does my role impact DS?
- How can I assess my organisation's status (tool)?
- How do I fix the problems relating to my role

Audience

- Senior Management
- Functional Management

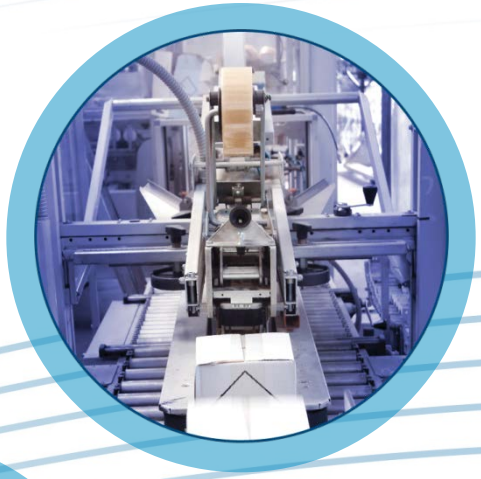
Advancement

- Different versions of the Tool (e.g. electronic)
- Trials with individual companies to prove benefit and help focus the tool
- Contact with sites highlighted by NCA shortage web sites to use tool and publish improvements for others to learn from
- ???...suggestions

Connecting a World of Pharmaceutical Knowledge

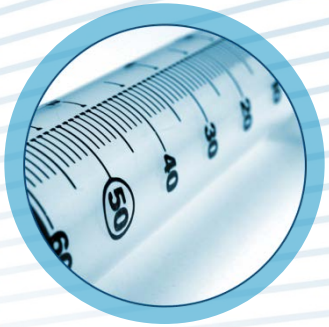
Connecting People, Science and Regulation®

PDA's Risk-Based Prevention & Management of Drug Shortage



EMA Workshop
London October 09, 2015

Emma Ramnarine
Stephan Rönninger
Georg Roessling
Anders Vinther



PDA's Approach to Preventing and Managing Manufacturing Quality Related Drug Shortages

- **Guiding principle – sustainable availability of drug products for patients**
  - Minimise risk for a manufacturing & quality related drug shortage through early assessment and evaluation in a structured way
- **A simple and straightforward concept**
  - Product-focused prevention and response plan
  - Harmonised terminology to facilitate common understanding globally
  - Goes 'hand-in-hand' with the EFPIA/EGA communication model and EMA communication tool
- **Ready to use PDA risk triage model**
  - Proactive identification of potential risks of a shortage
  - Simple procedures to assess and control risks
  - Issue escalation to management for decision making
  - Early communication to regulators - meet current notification requirements
- **Involvement of diverse & very competent PDA membership as well as many regulators**

Product Level Assessments

Risk-based triage approach

1. Risk-based triage of products

How to establish preventive controls based on product criticality and patient impact

2. Establish a Drug Shortage Risk Register & a Prevention and Response Plan

A holistic framework and simple templates at a product level

Patient impact first

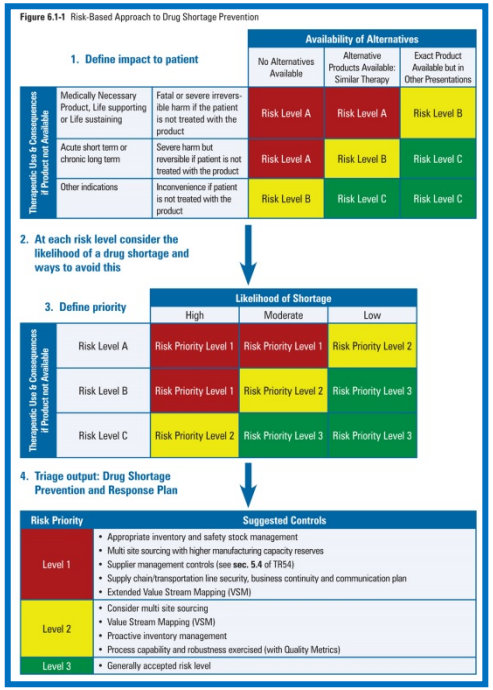


Figure 6.1-1 Risk-Based Approach to Drug Shortage Prevention

1. Define impact to patient

Therapeutic Use & Consequences if Product not Available	Availability of Alternatives: No Alternatives Available	Alternative Products Available: Similar Therapy	Exact Product Available but in Other Presentations
Medically Necessary Product, 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

2. At each risk level consider the likelihood of a drug shortage and ways to avoid this

3. Define priority

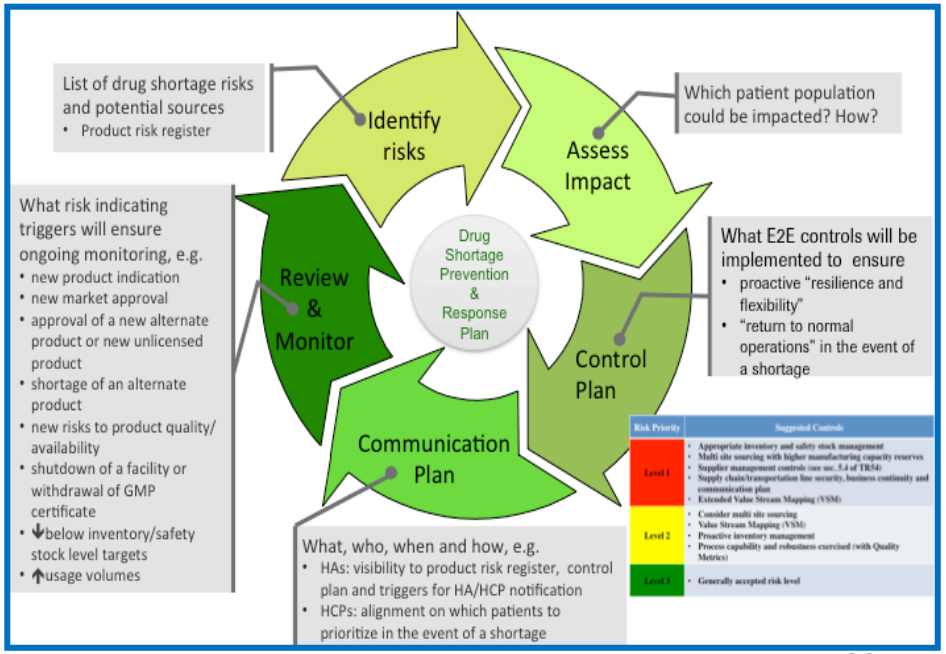
Therapeutic Use & Consequences if Product not Available	Likelihood of Shortage: High	Moderate	Low
Risk Level A	Risk Priority Level 1	Risk Priority Level 1	Risk Priority Level 2
Risk Level B	Risk Priority Level 1	Risk Priority Level 2	Risk Priority Level 3
Risk Level C	Risk Priority Level 2	Risk Priority Level 3	Risk Priority Level 3

4. Triage output: Drug Shortage Prevention and Response Plan

Risk Priority	Suggested Controls
Level 1	• Appropriate inventory and safety stock management • Multi site sourcing with higher manufacturing capacity reserves • Supplier management controls (see sec. 5.4 of TR54) • Supply chain/transportation line security, business continuity and communication plan • Extended Value Stream Mapping (VSM)
Level 2	• Consider multi site sourcing • Value Stream Mapping (VSM) • Proactive inventory management • Process capability and robustness exercised (with Quality Metrics)
Level 3	• Generally accepted risk level

Drug Shortage Risk Register

Drug Shortage Prevention and Response Plan



Risk-based Prevention, TR-68

Would the Concept Have Worked? - Example

1. Orphan Drug manufacturer

– Expressed success in using the risk-based tool to proactively think about alternative component suppliers, as components are often single-sourced

2. Prevent a drug shortage situation in the EU?

Situation
- Products are manufactured in EU and US and approved only in the respective countries
- The registration is identical, except for testing is according to USP (in US) and EP (in EU)

What happened
- Site in the EU has had a serious issue and stopped manufacturing

Issue
- Products from the US site could not be used in the EU since the US site was not approved by EU, which caused a drug shortage in the EU

Solution
- EMA approved 5 products in EU from the US site in act of emergency
- This took a lot of efforts and resources incl. managing the drug shortage

What could have been done

Using the tools might have proactively identified the gap in registration and to file the site in US as back up for EU (& vice-versa)

Free Access to PDA Products

Risk Management Tools

- The Risk Triage Model from TR 68.
- Template: Drug Shortage Risk Register - Appendix A of TR 68.
- Template: Drug Shortage Prevention and Response Plan - Appendix B of TR 68.

www.pda.org/DrugShortage

Conferences and training opportunities are being scheduled. For details see:
Additional Resources relation to the subject

TR 68 is part of a number of PDA Drug Shortage prevention activities

Drug Shortage – the work continues….

It's more than 'just' manufacturing & quality issues

Training on the Technical Report

Quality System and Risk Management

Manufacturing Science Workshop

Post-approval Change Management

PDA continues to work on preventing drug shortages

PDA Continues its Leadership on QRM Implementation…

~500+ members active in PDA QRM Interest Group

PDA QRM Interest Group *(driving active dialog in the industry on QRM implementation & realization)*

PDA TR 44
QRM General Principles & Case Studies for Aseptic Processes

PDA TR 54
Implementation of QRM for Pharmaceutical & Biotech. Manufacturing Operations

PDA Journal Articles
on risk-based Auditing
a) GxP Requirements along the Product Lifecycle, b) the process

QRM implementation surveys via Interest Group
Focus on QRM maturity

PDA TR 54-2
Case Studies for Packaging and Labeling

PDA TR 54-3
Case Studies for Drug Product (liquids and solids)

PDA TR 54-4
Case Studies for Biotechnology Manufacturing Operations

PDA TR 54-5
Risk Based Approach Preventing & Managing Drug Shortages

PDA TR 60
Process Validation

PDA TR 58
Technical Transfer in the PV life cycle approach

PDA TR 59
Statistical Methods for Production *& IG formed*

PDA TR 64
QRM for temperature controlled distribution

Regular 2-day PDA training workshops for TR54 series + 1-day PDA training workshops on TR68

Special Focus: Prevention of Drug Shortages *(PDA Task Force active since 2012)*

2013: Drug Shortages Presentations and discussions at PDA FDA Joint Conference

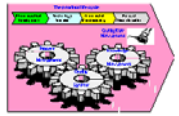
2014: Drug Shortages Presentations and discussions at Annual PDA Conference

April 2014:PDA Letter Article on risk based prevention of Drug Shortages April 2014

September 2014: Drug Shortages Workshop at PDA FDA Joint Conference

- PDAs Strategic Project of PCMO® covered QRM topics holistically; represents interest of a significant population of our membership in task forces, interest groups, conferences, trainings & workshops
- PDA deliverables developed in consensus by active volunteers from industry and Health Authorities, peer reviewed and approved by the Board of Directors after thorough review to ensure high quality state-of-art content

Paradigm Change in Manufacturing Operations®



Product Focused Risk-based Prevention

For practical implementation globally

Seville, Spain

Istanbul, Turkey

Philadelphia, US

Pretoria, South Africa

Seoul, Korea

Tokyo, Japan

Every Patient, Every Dose, Every Time

Questions from the Task Force

Communication

- Can EMA and NCA regulators establish a harmonised terminology and clear definitions on shortages?
- What is the EMA's and NCA's opinion and feed back on the products coming from the Inter-Association task force? Have they been assessed by EMA and NCAs?
- What initiatives will EMA and NCAs take to improve the communication process in EU for potential supply disruptions?
- How are regulators within the EU harmonising their approach to communicating the use of the deliverables of the Inter-Association team for drug shortages?
- What are regulators (EMA & NCAs) doing to increase the awareness of manufacturing and marketing authorisation holders responsibility in this area and the importance of this issue to patients?

Supply chain resilience

- What tools are EMA and NCAs going to use at the registration stage and/or GMP -inspections when looking for supply chain resilience? Whether NCAs will inspect not only at the MIAH but also at the MAHs as well?
- How can industry help to ensure the harmonised expectations at the inspections when supply chain resilience is evaluated?

Acknowledgements and Discussion

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 national competent authorities. We collectively commit to continue working through our associations to best serve patients through the complementary nature of our individual efforts.

Questions?

AESGP efpia EGA ISPE PDA Parenteral Drug Association PPTA

Further information

Communications principles

http://www.efpia.eu/uploads/Industry_Communication_Principles_Principles_Dec2014_Final_v1.pdf

Prevention

- **PDA technical report TR68**
  - https://www.pda.org/scientific-and-regulatory-affairs/regulatory-resources/drug-shortage
- **ISPE drug shortages survey and drug shortages prevention plan**
  - http://www.ispe.org/drug-shortages-initiative