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SCIENCE MEDICINES HEALTH

EMA perspective on Quality Metrics

Indian Pharmaceutical Alliance Annual Congress, Mumbai India

Presented by Brendan Cuddy on 24 February 2017
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Manufacturing and Quality – global issues we are seeing?

- Non-compliant sites; basic failings observed including due to data integrity issues;

Can the higher risk sites be identified and more closely supervised?

- Known problems in development getting through the market – failures in technology transfer; product recalls.
  - Lack of continuous improvement;
  - Lack of investment;
  - Poor quality interactions / communication between the industry and the regulator;

Can the industry adopt state of the art in QMS / manufacturing science?

Manufacturing and Quality – global issues we are seeing?

- Potential or actual shortages due to manufacturing and quality problems;
  - Lack of supply chain resilience;
  - Lack of proactivity in risk-assessment and risk mitigation measures;
  - Reduction in manufacturing capacity; alternatives not filed in Marketing authorisation;

How can increased risk of future shortages be identified / mitigated?

Quality Metrics and Europe

- "Quality Metric like data" is collected and reviewed during EU inspection, facilitating risk based inspection planning;

- EU authorities have sought industry engagement on preventing shortages of medicinal products.

We are very interested in:

- Learning more
- Starting a healthy international debate on Quality Metrics
- Discussing the consequences of Quality Metrics in a more global context.

What "Quality Metric like data" is available to inspectors?

Post-authorisation information:

- Recalls
- Quality defects
- PV signals
- Withdrawals/Shortages (due to GMP issues)
- Testing results
- Criticality to supply chain

Review of onsite data (e.g. PQR):

- Includes many if not all of the data outlined in FDA guidance
- Process validation reports

Product Quality Review
(inter alia)

- Supply chain traceability of active substances
- OOS and trending
- Other deviations or non-conformances
- Changes to processes and/or analytical methods
- MA variations
- Stability monitoring results
- Quality-related returns and complaints
- Corrective actions

EU approach to risk-based inspection scheduling

- Application of a risk-based approach to scheduling of inspections in the EU operational for many years.

- Legal basis: Directive 2001/83 Article 111.1b “inspections at an appropriate frequency based on risk”.

- Formal harmonised EU approach agreed in 2013 and a procedure on how to apply a risk-based approach to scheduling of inspections now published on the EMA website.

EU approach to risk-based inspection scheduling

- Complexity of the site
- Criticality of products/testing/service

EU/FDA approaches to risk-based inspections scheduling: comparison

- Risk-based decisions are made based on data **gathered through inspection.**

- Risk-based approach, will rely at least partially, on data **submitted by companies**.

EMA involvement in medicine shortages linked to GMP

22 November 2012
EMA/590745/2012
Patient Health Protection

Reflection paper on medicinal product supply shortages caused by manufacturing/Good Manufacturing Practice Compliance problems

2013

- 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)

EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL
Public Health and Risk Assessment
Pharmaceuticals

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Procedure for dealing with serious GMP non-compliance requiring co-ordinated measures to protect public or animal health

Volume 4
EU Guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

Part 1
Chapter 8: Complaints, Quality Defects and Product Recalls

2015

Implementation plan 2012-2015

2012

Medicine shortages
Shortages catalogue

2014

What have industry associations done?

A positive response

- Formed an Inter-Association Task Force
- 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

ISPE efpia PDA EGA AESG

08 October 2013
EMA/INS/GMP/461767/2013

Workshop on product shortages due to manufacturing and quality problems: Developing a proactive approach to prevention

21 December 2015
EMA/679967/2015
Stakeholders and Communication Division

Developing a proactive approach to the prevention of medicines shortages due to manufacturing and quality problems

Report from a stakeholder meeting at the European Medicines Agency - 9 October 2015

Risk Indicators for Shortages

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Risk indicators for Shortages (Manufacturing and Quality)

Nr.	Item	Yes	No	Comments
1	There is only a single manufacturer of the API registered			
2	There is only a single manufacturer of Finished Product registered			
3	Location of the Manufacturing Site(s) cause any concern? [i]			
4	One or more manufacturing sites have a marginal level of GMP compliance or are subject to increased inspection surveillance. (link to EudraGMDP and potentially risk based classification) [ii]			
5	There is a high product concentration at the finished product manufacturing site[iii]			
6	End to End Manufacturing process has long lead/holding times and/or extended supply chain;			
7	Manufacturing methods are complex, with capacity bottle necks in production;			

Nr.	Item	Yes	No	Comments
8	The manufacturer has had previous problems with quality defects and/or recalls.			
9	The manufacturer has had previous problems with supply.			
10	The medicinal product would meet the criteria of critical[iv]			
11	A design/device feature of the medicinal product could potentially prohibit switching patients.			

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

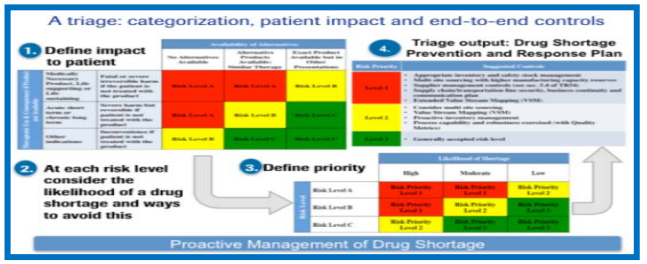
Features

- Follows ISPE's unique 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.

PDA Risk-Based Prevention of Drug Shortage

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.



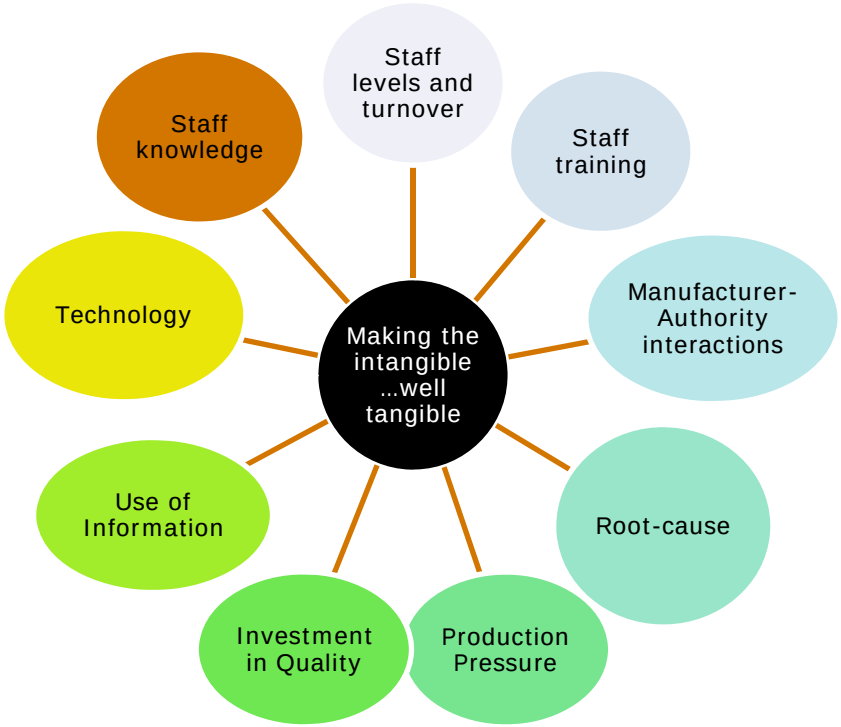
2.

Quality culture – key signs

How can quality culture be assessed?

Eudralex Volume 4, Part I, Chapter II:

"The correct manufacture of medicinal products relies upon people."



What makes a company excellent? (1/2)

Prepared

- Are you proactive in picking up evidence of a developing problem or only reacting after the problem has become significant?
- Can you detect signs of increasing risk especially if production pressure is increasing?
- How do you get top management to engage?
- How do you encourage staff to take ownership for quality and good behaviour?

Transparent – How do you increase transparency

- Do you identify and monitor vulnerabilities ?
- To what extent is information about quality/compliance problems shared within your organisation?
  share within your supply network?
  shared with regulators ?
- How do you encourage staff dealing with suppliers to focus on the aspects that really matter, as opposed to price?

What makes a company excellent? (2/2)

Flexible – adapting to change?

- How do you adapt to change, disruptions and opportunities?

- Is your supply chain resilient and robust?

- Can you invest in quality at those times when it appears to be unaffordable?

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Thank you for your attention

Further information

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