EMA perspective on Quality Metrics

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Presented by Brendan Cuddy on 24 February 2017
Head of Manufacturing and Quality Compliance, European Medicines Agency
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

Compliance-related risk
Intrinsic risk
Risk-rating

Recommended re-inspection frequency
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.
## Risk Indicators for Shortages

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Item</th>
<th>Yes</th>
<th>No</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>There is only a single manufacturer of the API registered</td>
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<tr>
<td>2</td>
<td>There is only a single manufacturer of Finished Product registered</td>
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<td>3</td>
<td>Location of the Manufacturing Site(s) cause any concern?</td>
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<td>4</td>
<td>One or more manufacturing sites have a marginal level of GMP compliance or are subject to increased inspection surveillance. (link to EudraGMDD and potentially risk based classification)</td>
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<td>5</td>
<td>There is a high product concentration at the finished product manufacturing site</td>
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<td>6</td>
<td>End to End Manufacturing process has long lead/holding times and/or extended supply chain;</td>
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<td>7</td>
<td>Manufacturing methods are complex, with capacity bottle necks in production;</td>
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<td>8</td>
<td>The manufacturer has had previous problems with quality defects and/or recalls.</td>
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<td>9</td>
<td>The manufacturer has had previous problems with supply.</td>
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<td>10</td>
<td>The medicinal product would meet the criteria of criticality</td>
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<td>11</td>
<td>A design/device feature of the medicinal product could potentially prohibit switching patients.</td>
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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
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?
Thank you for your attention

Further information

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