EFPIA Good Practice – Revision 1, October 2014

Reducing Risk of Drug Products Shortages

Introduction

Authorities, industry and healthcare providers have a responsibility to ensure a modern and sustainable healthcare system in Europe in order to provide patients with equal and early access to the best and safest medicines.

The pharmaceutical industry continues to establish increasingly robust quality and business management practices including holistic quality management systems, market forecasting methods and inventory management techniques. The successful implementation of these practices in an integrated manner is critical for patients to rely on a continued supply of quality medicines. A proactive management system that actively assures and monitors quality standards, inventory levels and market signals is recommended for successful supply management to be achieved.

EFPIA member companies do recognise the importance of working towards preventing drug shortages and effectively managing supply before a shortage actually occurs. A management system itself can minimise the risks of drug product supply disruptions from arising, and EFPIA member companies have shared practices and developed this ‘good practice’ guide. The guide aims to describe the principles of a “management system” approach to reducing risks, by promoting the management of quality and supply logistics, the use of risk management practices and the management of drug product supply disruptions, should they occur. These principles can either be employed proactively when the risk of drug shortage results from a situation internal to the company as well as reactively when it results from a market situation which was not foreseeable based on the company’s internal indicators results and trends.

Availability of medicines to patients is as important as safety and efficacy of the medicines and shortages of drug products have become a growing concern for regulatory authorities, patients and healthcare providers. Disruption in the supply of medicines impacts both patients and clinicians directly and can result in interruptions of on-going therapies, the use of alternative, unfamiliar or less suitable medications or even outright failures to treat.

Risk awareness, proactive monitoring and effective and timely communication are critical to the successful management of drug product supply and, importantly, shortage situations should these occur (Figure 1).

\[1 \text{ product supply disruptions (US) / abnormal restriction in supply (EU) (convergence in terminology)}\]
Figure 1: Communication /Information Flow about Disruptions in Supply and Drug Shortages

Figure 2 and Table 1, below, describe a ‘good practice’ model that a company can adopt to prevent and / or manage supply disruptions. It is based on the key principles that:

- Drug product supply disruption management is an integral part of the supply organisation,
- A holistic view of the supply chain (end-to-end) is established, and
- Risk management is applied to identify root causes and to prioritise mitigation actions.

Potential Drug Shortage

For the purpose of this good practice model, a potential drug shortage\(^2\) is described as the occurrence of internal or external situations (single or in a combination of both), which could result in an interruption of supplies of a medicinal product, if not properly addressed and controlled. Such potential drug shortages very often arise from special cause problems.

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\(^2\) Note that EFPIA has previously proposed the definition for drug shortages as "A crisis situation caused by the inability of any Marketing Authorisation Holder to supply a drug with a specific Active Pharmaceutical Ingredient to a market over an extended period of time resulting in the unavailability of this medication for patients."
Good Practice Principles

Figure 2: Prevention of Drug Product Supply Disruptions through a Supply Management System

Legend

- Proactive Quality Risk Management
- Reactive Quality Issue Management

1. Set up a Supply Management system
2. Identify all potential root causes of Drug Shortage
3. Define and implement risk control strategies
4. Assess impact on drug availability
5. Risk of supply disruption?
   - Yes
   - No
5a. Update the Root causes catalogue
   - Yes
   - No
6. Initiate management process of the supply disruption risk
7. Implement mitigation solutions
8. Actual disruption in supply?
   - Yes
   - No
8a. Take counter measures to minimise the impact of the disruption in supply
9. Implement CA/PA solutions for prevention of recurrences
10. Close and inform about closure of the supply disruption management process
11. Close the supply disruption management process
Table 1: Good Practice Steps to Prevent or manage Potential Drug Shortage Situations

<table>
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<tr>
<th>Step</th>
<th>Responsibilities</th>
<th>Details on process</th>
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| **Set up a Supply Management System** | • Top management  
• Quality Unit | - Clear commitment from the Top management to prevent supply disruptions  
- Integration in the Company’s Quality Systems of metrics, communication channels (internal and external with Stakeholders) and improvement measures to prevent supply disruptions  
- Should involve all supply chain actors |
| 1. Identify all potential root causes of Drug Shortage |  |
| 1A: Market Dynamics Risks | • Distribution management | - Compare the plan for demand versus actual capabilities  
- Establish KPI, e.g. for:  
  o Estimated coverage of demand  
  o Actual coverage of demand  |
| 1B: Up-Stream supply chain Risks | • Sourcing management | - Establish long term plan for the sourcing in order to cover the productions needs  
- Establish KPI e.g. for:  
  o Number of batches postponed  
  o Estimated coverage of supply  
  o Actual coverage of supply  |
| 1C: Down-stream distribution Risks | • Distribution management  
• Quality Unit | - Establish KPI e.g. for:  
  o Number of batch rejected due to distribution issues  |
| 1D: Drug product manufacturing system risks | • Manufacturing management  
• Quality Unit | - Establish KPI e.g. for number of batch rejected due to non-conformances  |
| 2. Define and implement risk control strategies | • All supply chain actors coordinated by downstream supply chain management | - Define action and alert levels for each supply, manufacturing and distribution activity.  
- Define the possible control strategies covering the different identified causes.  
- Establish communication links for the control strategy  
- Implement and review the strategies efficiency  |
| 3. Survey the market situation | • All supply chain actors coordinated by downstream supply chain management | Monitor:  
- Monitor 1A, Shift in the Market Situation  
  o Demands from wholesalers and pharmacies  
  o Competition from generics, biosimilars or new innovations  
- Monitor 1B, Upstream Supply Chain  
  o Performance and quality measures  
- Monitor 1C, Down Stream Supply Chain  
  o Performance and quality measures  
- Monitor 1D, Manufacturing System  
  o Performance and quality measures |
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| 4. Assess impact on drug availability | - All supply chain actors coordinated by downstream supply chain management | - Assess data from step 3 to identify potential shortage situations  
- Adjust supply chain throughput in reaction to monitoring results, when alert limits are reached, as needed  
- Initiate CAPA when alert limits are reached  
- Adjust control strategy, alert and action limits according to Business Decisions  
  o Capacities  
  o Opportunities  
  o Changes |
| 5. Risk of supply disruption | - All supply chain actors coordinated by downstream management | - Communicate the risk for disruption in supply to ensure top management involvement initiate management process step 6  
- Initiate or enhance CAPA when action limits are reached |
| 6. Initiate management process of the risk of supply disruption | - Dedicated task force, with top management steering function | - Detailed problem and risk analysis, derive risk control options, including business decisions, as needed |
| 7. Implement mitigation solutions | - Dedicated task force, with top management steering function | - Execute risk control measures, including communication plan |
| 8. Actual disruption in supply? (decision point) | - Dedicated task force, with top management steering function | - Management approval of risk control measures and communication plan, incl. notification of authorities, as necessary |
| 9. Mitigate the impact of the actual disruption in supply | - Dedicated task force, with top management steering function | - Continue risk control measures and measures to minimize impact of shortage; review business decisions, as needed |
| 10. Implement CAPA solutions for prevention of recurrence | - Dedicated task force, with top management steering function | - Close improvement / prevention measures through CAPA system |
| 11. Close the supply disruption management process | - Top Management with input from the assigned task force | - Management review step to determine success of risk control measures  
- Take formal decision to conclude the process |

**KPI:** Key Performance Indicator  
**CAPA:** Corrective Action and Preventive Action
### Product shortage due to manufacturing constraints

5.71 The manufacturer should report to the marketing authorisation holder (MAH) any constraints in manufacturing operations which may result in abnormal restriction in the supply. This should be done in a timely manner to facilitate reporting of the restriction in supply by the MAH, to the relevant competent authorities, in accordance with its legal obligations.

* Articles 23a and 81 of Directive 2001/83/EC

### Principle

All concerned competent authorities should be informed in a timely manner in case of a confirmed quality defect (faulty manufacture, product deterioration, detection of falsification, non-compliance with the marketing authorisation or product specification file, or any other serious quality problems) with a medicinal or investigational medicinal product which may result in the recall of the product or an abnormal restriction in the supply. In situations where product on the market is found to be non-compliant with the marketing authorisation, there is no requirement to notify concerned competent authorities provided the degree of non-compliance satisfies the Annex 16 restrictions regarding the handling of unplanned deviations.

In case of outsourced activities, a contract should describe the role and responsibilities of the manufacturer, the marketing authorisation holder and/or sponsor and any other relevant third parties in relation to assessment, decision-making, and dissemination of information and implementation of risk-reducing actions relating to a defective product. Guidance in relation to contracts is provided in Chapter 7. Such contracts should also address how to contact those responsible at each party for the management of quality defect and recall issues.