efpia
European Federation of Pharmaceutical Industries and Associations

EFPIA Good Practice – October 2013

Reducing Risk for Drug Products Shortages

Introduction

Authorities, industry and healthcare providers have a responsibility to ensure a modern, 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 to ensuring that patients can 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.

A management system itself can minimise the risks but can never completely prevent drug shortage situations arising and EFPIA member companies do recognise the importance of working to avoid drug shortages and effectively managing them if they do occur. As a consequence member companies have shared practices and principles and developed this 'good practice' guide. The guide is intended to describe the principles of a “management system” approach to reducing drug shortage risks by promoting proactive management of quality and supply logistics, use of risk management practices and proactive management of shortage situations 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.

An awareness of the risks, proactive monitoring and effective and timely communication are critical to the successful management of drug product supply and, importantly, shortage situations if they occur (Figure 1).

Fédération Européenne
d’Associations et d’Industries
Pharmaceutiques

Leopold Plaza Building
Rue du Trône 108 Boîte 1
B-1050 Bruxelles

T +32 2 626 25 55
F +32 2 626 25 66
www.efpia.eu

TVA BE.418.762.559

Figure 1: Information Flow about Drug Shortages

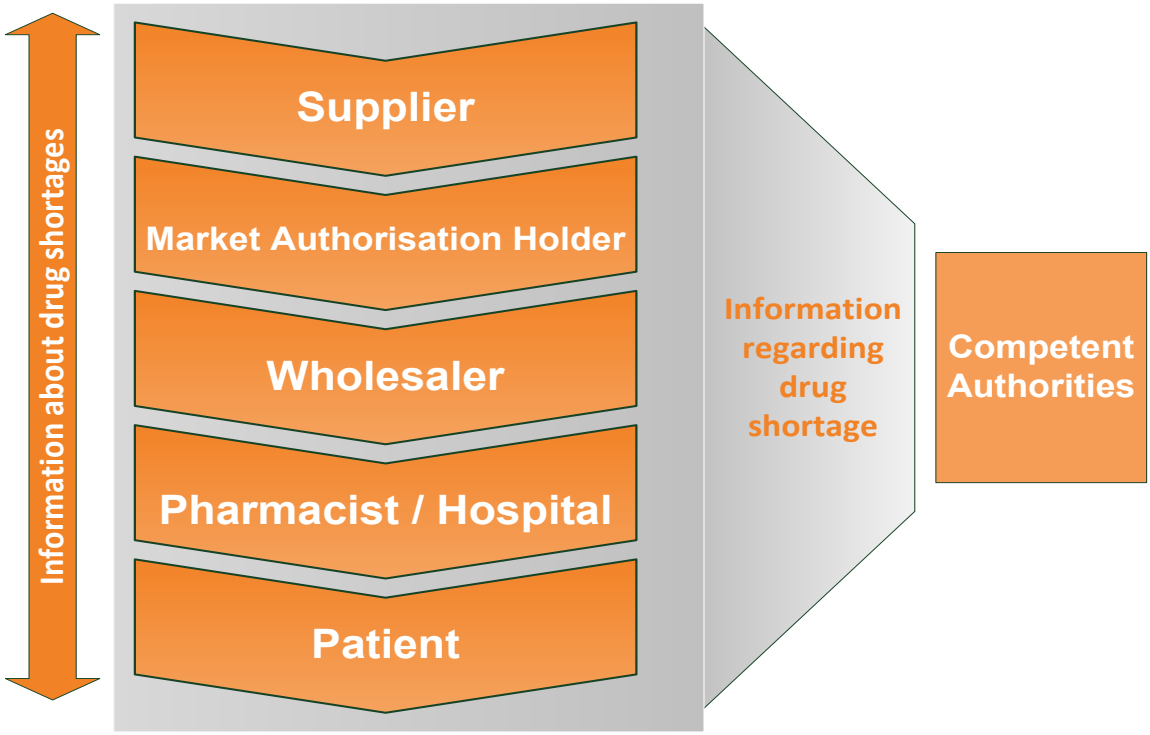

Figure 2 and Table 1, below, describe a 'good practice' model that a company can adopt to prevent and / or manage potential drug shortage situations. It is based on the key principles that:

- Drug shortages 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[1] 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.

[1] 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 Shortages through a Management System

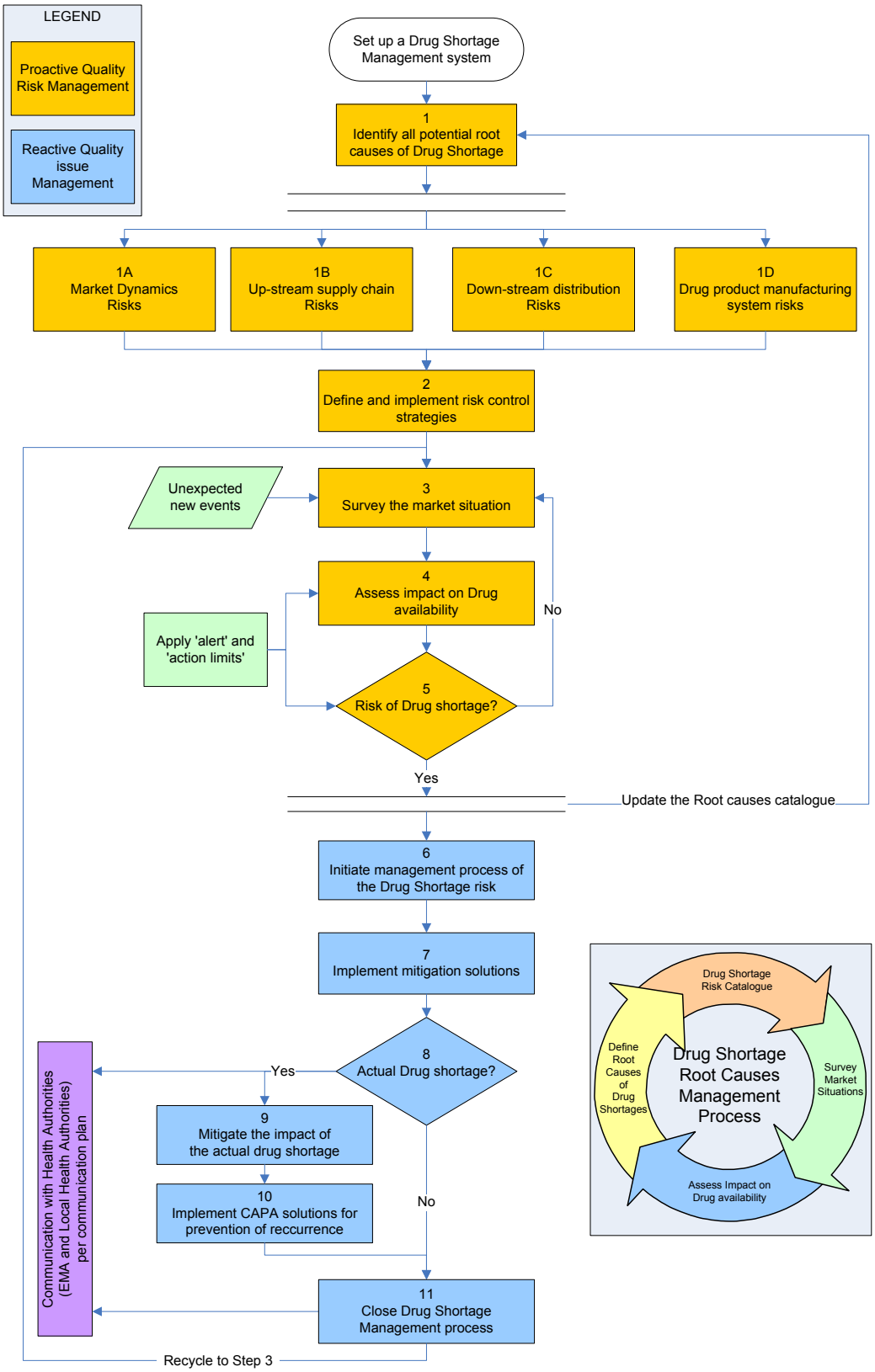

Table 1: Good Practice Steps to Prevent or manage Potential Drug Shortage Situations

Step	Responsibilities	Details on process
Set up a Drug Shortage Management System	• Top management • Quality Unit	- Clear commitment from the Top management to prevent the drug shortages - Integration in the Company's Quality Systems of metrics, communication channels (internal and external with Stakeholders) and improvement measures to prevent drug shortages - Should involve all supply chain actors
1. Identify 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	<u>Monitor</u>: - 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

Step	Responsibilities	Details on process

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
		  ○ Capacities
		  ○ Opportunities
		  ○ Changes

5. Risk of drug shortage	• All supply chain actors coordinated by downstream management	- Communicate the shortage risk 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 Drug Shortage risk	• 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. Drug Shortage (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 drug shortage	• 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 Drug Shortage 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**: Knowledge Performance Indicator*
***CAPA**: Corrective And Preventive Action*

Regulatory framework

Directive 2001/83/EC

Article 23a	*If the product ceases to be placed on the market of a Member State, either temporarily or permanently, the marketing authorisation holder shall notify the competent authority of that Member State. Such notification shall, other than in exceptional circumstances, be made no less than two months before the interruption in the placing on the market of the product. The marketing authorisation holder shall inform the competent authority of the reasons for such action in accordance with Article 123(2).*
Article 81	*The holder of a marketing authorisation for a medicinal product and the distributors of the said medicinal product actually placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered.*
Article 123	*2. The marketing authorisation holder shall be obliged to notify the Member States concerned forthwith of any action taken by the holder to suspend the marketing of a medicinal product, to withdraw a medicinal product from the market, to request the withdrawal of a marketing authorisation or not to apply for the renewal of a marketing authorisation, together with the reasons for such action. The marketing authorisation holder shall in particular declare if such action is based on any of the grounds set out in Article 116 or Article 117(1).* *2a. The marketing authorisation holder shall also make the notification pursuant to paragraph 2 of this Article in cases where the action is taken in a third country and where such action is based on any of the grounds set out in Article 116 or Article 117(1).* *2b. The marketing authorisation holder shall furthermore notify the Agency where the action referred to in paragraph 2 or 2a of this Article is based on any of the grounds referred to in Article 116 or Article 117(1).* *2c. The Agency shall forward notifications received in accordance with paragraph 2b to all Member States without undue delay.*

EU GMP Part 1

Draft Chap. 5, Production	Product shortage due to manufacturing constraints: 5.68 "The holder of a marketing authorisation for a medicinal product should, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply medicinal products. The marketing authorisation holder should be informed in a timely manner in case of any constraints in manufacturing operations, which may result in an abnormal restriction in the supply of a medicinal product. The holder should also notify the competent authority if the product ceases to be placed on the market of the Member State, either temporarily or permanently. Such notification shall, otherwise than in exceptional circumstances, be made no less than 2 months before the interruption in the placing on the market of the product.
Draft Chap. 8, Complaints, Quality Defects and Product Recalls	Principle: all concerned competent authorities should be informed in case of a 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.