EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Patient Health Protection

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

1. Introduction

Ensuring the security and Good Manufacturing Practice (GMP) compliance of the manufacturing supply chain is an important responsibility of the Marketing Authorisation Holder (MAH) to ensure appropriate and continued availability of medicinal products for human use to meet the needs of patients in accordance with Article 81 of Directive 2001/83.

There is evidence that disruption in supply of medicines can lead to inter alia, a failure to treat; the use of less desirable, often expensive, unfamiliar alternative medicinal products; an increased potential for errors and poorer patient outcomes, caused by absent or delayed treatment or incidence of preventable adverse events associated with alternative medicinal products or dosage forms[1].

Recent unexpected disruptions to the manufacturing supply chain due to manufacturing/GMP compliance problems have resulted in acute and chronic shortages of important medicinal products in the European Union (EU) requiring changes to prescribing information, and initiation of patient allocation programs[2].

EU legislation currently requires mandatory pre-notification by MAHs of disruption of supply in the case of permanent or temporary cessations[3,4] and for manufacturers of medicines in the case of any defect that could lead to an abnormal restriction in supply[5].

In the United States (US), as a result of a high number of shortages of medicinal products, the Food and Drug Administration (FDA) have published at the end of last year a draft "Interim Rule" regarding

[1] ISMP Medication Safety Alert, Special Issue Drug shortages: National Survey Reveals High Level Of Frustration, Low Level Of Safety, September 23, 2010 issue.
[2] Shortage of Caelyx, 09 September 2011, EMA/718827/2011.
[3] Article 23 2001/83 Directive 2001/83/EC Of The European Parliament And Of The Council Of 6 November 2001 On The Community Code Relating To Medicinal Products For Human Use (as amended).
[4] Article 13 of 726/2004 Regulation (Ec) No 726/2004 Of The European Parliament And Of The Council Of 31 March 2004 Laying Down Community Procedures For The Authorisation And Supervision Of Medicinal Products.
[5] Article 13 of Commission Directive 2003/94/EC Of 8 October 2003 Laying Down The Principles And Guidelines Of Good Manufacturing Practice In Respect Of Medicinal Products For Human Use And Investigational Medicinal Products For Human Use.

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revised mandatory pre-notification requirements for manufacturers in case of potential drug shortages[6].

Other international partners including Health Canada (HC) and the Therapeutic Goods Administration (TGA) have indicated their interest in the area of product supply and their willingness to participate in a collaborative effort to share information about product supply issues.

2. Problem statement

This Reflection Paper is concerned with public health crises that arise due to unforeseen disruptions within the manufacturing process, caused by manufacturing/GMP compliance problems and affecting medicinal products for human use, independent of their route of authorisation, where a need for co-ordination of the assessment and risk reducing actions at a Community level has been identified. Supply disruptions not caused by manufacturing/GMP compliance problems fall outside the scope of this Reflection Paper. There has been considerable interest expressed at various fora within the EU Regulatory Network (hereafter referred to as the Network) in the topic of medicines supply shortages due to manufacturing/GMP compliance problems. The Committee for Human Medicinal Products (CHMP) in almost all plenary meetings throughout 2011 has discussed problems of continuity of supply caused by manufacturing problems in relation to certain medicinal products. The EU Good Manufacturing and Distribution Practice Inspectors Working Party (GMP/GDP IWG) has adopted in its February 2011 plenary meeting a concept paper for revising Chapter 8 of the GMP Guide "Complaints and Product Recall". The concept paper has identified that the management and minimisation of supply shortages that may arise as a result of quality defects should also be addressed in a revision of Chapter 8. The proposal, among other things, is to clarify reporting requirements relating to restriction of supply whether or not this relates to a quality defect[7].

While control and supervision of the national market remains a national responsibility, Member States may experience difficulties in acting in a purely national way when faced with a pan-European crisis. The Network is increasingly looking to the European Medicines Agency (EMA) to support the Network by co-ordinating the development and communication of appropriate risk management measures arising from unexpected shortages in supply. This coordination may be through informal cooperation and information sharing or formally through the initiation of Community procedures as a result of identified public health concerns where supply is affected.

Public health crises caused by shortages of medicinal products usually require centralised assessment by multi-disciplinary teams from within the Network, require the engagement of all stakeholders in the Network, frequently require the engagement of actors/experts inter-linked with, but not operating within the Network, usually need rapid and sophisticated communication of appropriate risk management measures, and may require an implementation that is customised to the national situation. The effects of these crises can be more enduring after the initial shock to the system and they may require short, medium and long term remediation measures to be taken both by industry, by the Network and by patients/healthcare providers.

This Reflection Paper summarises the lessons learned from previous crises where the EMA had a supporting or co-ordinating role, and presents short and mid-term actions that may allow the Network to prevent, mitigate, and manage shortages of important medicinal products.

[6] 21 CFR Part 314, Federal Register / Vol. 76, No. 243 / Monday, December 19, 2011 / Rules and Regulations.
[7] Concept paper on Revising Chapter 8 of the EC guide to GMP to introduce risk-based concepts and to provide for more effective investigations and CAPA actions.

3. Lessons learned

Over the past two to three years there have been a number of public health crises caused by acute and chronic supply shortages as a result of manufacturing/GMP compliance problems. Experience obtained has been analysed and a number of lessons learned have been identified. Although these shortages have been primarily in supply of medicines for human use, the lessons learned from these cases may also be applied to supply of veterinary medicines.

3.1. The regulators' dilemma

a) In some cases defective medicines had to be left on the market to prevent shortages of life saving medicines as there is no available alternative and the risks linked to a possible exposure with the defective product are considered less than those linked to the unavailability of the product.

b) In some cases of GMP non-compliance the ability of Regulators to take action against a manufacturing site was restricted in order to avoid product shortages. Very difficult risk-benefit judgements had to be made between poor quality processes or product, or no product at all.

c) The switching of patients to alternatives may also be hindered by factors other than supply per se and beyond the control of the Network. For example, the exclusive link between peritoneal dialysis solutions from a certain MAH, the patient and the connector meant the exclusion of competitor products so that patients were inextricably linked to products from that MAH and could not be switched without undergoing a surgical procedure to change the connector further increasing the risk to patients.

3.2. The impact of globalisation

a) The globalisation of manufacture has continued to increase in importance so that many medicinal products have extended manufacture and supply chains, which increases the risk of supply disruption including new vulnerabilities.

b) Many sources of active substances for life-saving medicines, e.g. antibiotics, are now wholly located outside the EU, some located in countries that have uncertain political and regulatory systems and which may be prone to natural disaster. The 2011 tsunami in Japan has illustrated how natural disasters can impact the supply chain of pharmaceuticals.

c) Manufacturing is in consolidation, leading to one or very few manufacturing sites supplying at a global level so failure at these sites leads to global supply shortages. There may be no redundancy or fail-safe capacity built into the global supply chain. We have seen the case of a single contract manufacturer with particular capabilities may be depended upon for several key products. With the arm's length involvement of the MAH, contract manufacturing can be prone to marginal GMP compliance and consequent potential quality problems leading to supply problems.

3.3. The industry's approach

a) The industry's risk management tends to be very reactive rather than proactive. Sustained pressure is needed to bring about a change in a manufacturer's approach to quality risk management and supply chain security.

3.4. The current regulatory framework

a) Unprecedented import of large quantities of unlicensed versions of medicines by Member States to prevent a shortage had to be supported by rapid and sustained pressure on MAHs to introduce variations to regularise the situation. The need for urgent variations or better still pre-planned inclusion of failsafe manufacturing site capacity in marketing authorisations needs to be considered.

b) Even if there are several potential suppliers at a global level only one or two may have been included in a given marketing authorisation to the EU. It, therefore, can be difficult to add these quickly in a time of crisis – all the more so in the case of biological medicinal products where there are greater regulatory hurdles as a result of concerns about the equivalence of product from different manufacturing sites.

3.5. Collaboration and cooperation within the Network

a) Actions at national level are taken to address local supply shortages without information being shared within the Network.

b) Proactive risk management and clear and transparent communication by the MAH are essential measures to maintain trust between all stakeholders.

3.6. The international dimension

a) International collaboration amongst Regulatory Authorities at a global level is vital to ensure better supervision of these globalised supply chains.

b) There may be a need to mobilise resources from outside the Network in order to assess problems and provide solutions.

3.7. Other aspects

a) The interfaces between medicinal products and other products such as medical devices can be important and there is a need for further discussion about how best these interfaces can be managed.

b) The existence of monopolies in supply of medicines restricts options for risk mitigation. There is a need for further discussion in order to address this issue.

4. Envisaged activities

While the causes of shortages are varied and complex, the challenge remains to effectively co-ordinate an assessment, to develop risk minimisation measures to alleviate the impact on patients, and to communicate within the Network, with international partners and with healthcare professionals, patients and the general public. On occasions EMA is being asked to coordinate the follow-up to an emerging event in the absence of an appropriate legal framework.

In some cases, the need for rapid implementation of risk minimisation measures is paramount. Short and medium term measures will be undertaken to enhance the current approach. In addition, there are some aspects which will require discussion with bodies outside the Network, e.g. in the area of medical devices.

4.1. Short term actions

1. Establish an internal catalogue of Centrally Authorised Products (CAPs) and non-CAPs requiring coordination at EU level (e.g. referrals) that have experienced product shortages to facilitate future analysis of trends and communication on shortages.
2. Maintain a public catalogue of current shortages of CAPs and medicinal products where an EU co-ordination of assessment has been undertaken with links to all relevant Opinions, communications, etc. MAHs will be invited to report shortages caused by manufacturing/GMP compliance problems on a voluntary basis.
3. Develop a common understanding of the concept of "essential" medicine for subsequent application at national level and develop a decision tree to assist National Competent Authorities (NCAs) in deciding what shortages should be dealt with at EU level (also providing clarification on the most appropriate regulatory framework to be applied).
4. Provide clarification on how to best provide national input into the development of EU advice/ communication and how such EU advice/communication and national advice/communication can be complementary.
5. Establish and publish a Standard Operating Procedure (SOP) for handling reports of shortages in supply of medicinal products due to quality defects and manufacturing problems and where an EU co-ordination of assessment is necessary. The procedure should outline the interlinking of regulatory, pharmacovigilance, GMP inspection, assessment and communication aspects of dealing with shortages due to unforeseen events in the manufacturing supply chain.
6. Revise through the GMDP IWG the Community Procedure "Procedure for Handling Rapid Alerts Arising From Quality Defects" to include transmission of alerts in the event of a shortage in supply of medicinal products due to quality defects and manufacturing problems, whilst ensuring that this will not result in non-urgent information being transmitted. Revise through the GMDP IWG Chapter 8 of the GMP Guide "Complaints and Product Recall" to clarify reporting requirements relating to restriction of supply in case this relates to a quality defect and a recall of batches.
7. Explore if "crisis" situations arising from shortages in supply of medicinal products due to quality defects and manufacturing problems can in the future also be addressed in the context of the EU Regulatory Network Incident Management Plan for medicines for human use.
8. Develop international co-operation in this area so that there is a sharing of information on specific shortages (with or without impact on other territories) and sharing of information on best practices on risk management and prevention strategies.
9. Raise the awareness of the impact of medicinal product shortages and stimulate industry reaction and improvements (whereby industry should propose solutions) in business continuity planning guaranteeing better access for patients to essential medicines by organising a public workshop between Regulatory Authorities, industry, patient and healthcare representatives to outline the problems encountered.
10. Undertake a survey of past initiatives taken by NCAs to manage/prevent shortages in order to develop an inventory of possible tools available to NCAs and to share best practice.

4.2. Medium term actions

1. Facilitate risk benefit evaluation where risk of shortage has to be balanced with potential risk due to presence of a product defect.
2. Promote better and proactive risk management by MAHs by requiring submission by all MAHs of a risk-analysis of their manufacturing process identifying any weaknesses and, depending on the severity, provide a contingency plan and proposals to strengthen the identified weaknesses.
3. Investigate processes that could be used to measure the impact of medicinal product shortage in patients experiencing its consequences, e.g. lowered dose or switch to an alternative product.

The Implementation Plan 2012-2015 for such actions can be found under Doc. Ref.: EMA/708575/2012.