



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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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

### 1. Introduction

Shortages of medicines have been a global problem for the past decade and have also increasingly affected the European Union (EU) with significant impact on patient care. The causes of medicine shortages are varied and include economic, business, political, manufacturing and distribution issues. However, the European Medicines Agency (hereinafter the Agency) is mainly involved with shortages due to manufacturing or Good-manufacturing-practice (GMP) compliance problems. In 2012, the Agency published a reflection paper concerning public health incidents arising from manufacturing disruptions linked to problems such as quality defects or GMP compliance issues<sup>1</sup>. The paper summarises the lessons learned from previous crises and presents short and mid-term actions that may allow the EU regulatory network to prevent, mitigate and manage shortages of important medicinal products.

In 2013, the Agency organised an initial public [workshop on product shortages due to manufacturing and quality problems](#) in order to raise awareness of the impact of shortages and to promote better and proactive risk management by companies. Following the workshop, an inter-association task force was established with representatives of industry. The aim of this task-force was to develop tools to support manufacturers and marketing authorisation holders in preventing and communicating disruptions in the supply chain due to GMP non-compliance/quality defects.

In addition, based on the implementation plan and input gathered at the October 2013 workshop, the Agency developed a set of documents to support medicines regulators involved in the EU-level coordination of shortage situations due to GMP non-compliance/quality defects:

- [criteria for classification of critical medicines](#)
- [facilitation of benefit-risk assessment through a defined common assessment report](#)



- [points to consider for the overall assessment of a medicine shortage due to GMP non-compliance/quality defects](#)
- [identification of risk indicators for shortages](#)
- [decision tree to help decide whether a particular national shortage should be escalated to European level](#)
- [information sources for issuing treatment recommendations during medicines' shortages](#)
- [public catalogue of shortages](#)

On 9 October 2015, the Agency convened a second stakeholder meeting bringing together national competent authorities, industry and patient and healthcare professional representatives to discuss recent initiatives and to reflect on possible further actions to proactively manage shortages. The workshop was divided into three parts. The first part was only attended by representatives from national competent authorities and was used to provide an overview on the way shortages are managed across the EU regulatory network. The second part included representatives from industry associations (professional and trade) and patient/healthcare professional associations in addition to representatives from national competent authorities. During this part speakers gave short presentations on the impact of shortages and approaches to their management. This second part was followed by individual break-out sessions:

1. Definition of shortage and possible metrics.
2. Causes of supply chain disruptions (related to good distribution practice).
3. Implementation of inter-association tools by industry.
4. Communication of shortages (between industry and regulators and between regulators, and to healthcare professions and patients).

Feedback of the break-out sessions would be used to update the shortage implementation plan. The third part with representatives from national competent authorities was used to agree on a common approach amongst regulators. The sessions attended by all stakeholders groups are available [here](#).

## 2. Discussion on current situation

### ***2.1. How do EU competent authorities address shortages of medicines?***

In an effort to identify best practices in the way medicine shortages are notified and handled at European level, the Agency carried out a survey amongst Member States in August 2015. The results of the survey showed that although there is no harmonised approach to reporting and dealing with shortages, common points could be identified which could be built on to develop common best practices for national competent authorities. The survey found that mandatory notification for shortages was a requirement for most Member States (21 out of 28 that responded to the survey). Although there is no EU-wide template for notifications the information required by individual Member States is similar and some overlap was observed. The survey highlighted that most Member States do not have a definition for a shortage (18 out of 28 responses). The lack of a common definition was highlighted several times during the workshop as an obstacle for a common approach in dealing with shortages. This lack of clarity about what a shortage is means that the conditions for reporting

shortages differ from one country to another which makes benchmarking and comparisons very difficult.

The survey showed that once identified, shortages are very much dealt with on a case by case basis and strategies include importation of medicines from other markets, controlling the export of the affected medicine, working with the marketing authorisation holder to resolve the causes that led to the shortage and issuing marketing authorisation exemptions.

## **2.2. Feedback on industry deliverables**

Following the 2013 workshop and the Agency's request to industry to provide solutions to the global problem of medicines shortages, an inter-association task force was created which comprised members from:

- International Society for Pharmaceutical Engineering (ISPE)
- Parenteral Drug Association (PDA)
- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- Association of the European Self-Medication Industry (AESGP)
- The European Generic medicines Association (EGA)
- Plasma Protein Therapeutics Association (PPTA)

In addition, a task force was established with two complementary work streams agreed with the Agency. One, led by the trade associations EFPIA, EGA, AESGP and PPTA addressed harmonised communication principles between industry and authorities for quality- and manufacturing-driven supply disruptions. The document "Quality and manufacturing driven supply disruptions: industry communication principles to Authorities" provides guidance for streamlining and harmonising reporting requirements<sup>2</sup>. It includes suggestions for common criteria for triggering notification based on an agreed definition of a supply disruption, and a triage process that evaluates the risk associated with a potential supply disruption; a harmonised content and format of reports, and an agreed time point and recipient of the information for all nationally and centrally approved products.

The other work stream involved the associations PDA and ISPE, who worked together on the charter "to deliver a proposal and plan that address the prevention of drug shortages due to manufacturing Quality Issues". ISPE developed the "Drug Shortages Assessment and Prevention Plan" to aid manufacturers in assessing their preparedness for preventing or managing a supply disruption<sup>3</sup>. ISPE's systems based approach is responsive to the root causes of manufacturing and quality issues and is founded on the six dimensions necessary to obtain operational success and avoid shortages. It contains recommendations for each dimension: corporate quality culture, robust quality system, metrics, business continuity planning, communication with authorities and building capability and helps to address shortages on a global basis.

PDA on the other hand developed a complementary "Risk-Based Approach for Prevention and Management of Drug Shortages", which provides a holistic risk-based framework at a product level for prevention of shortages, a risk triage model that can be used to assess drug shortage risks and implement appropriate controls, as well as templates for a Drug Shortage Risk Register and a Drug Shortage Prevention and Response Plan<sup>4</sup>. The templates provided help to systematically and proactively identify potential risks to product supply in the end-to-end value chain for a product,

prioritise risk mitigation activities and use the outputs to engage in proactive dialogue with health authorities.

The associations highlighted that although they had met the deliverables set out in the 2013 implementation plan by providing tools to build more resilient supply chains and to establish more effective communication processes, these tools now need to be implemented. An important aspect will be the sharing success stories and the measuring of the impact of the tools provided. The industry associations pointed out that successful resolution of shortages would require developing tools and solutions for all actors in the supply chain and to extend the scope of shortages to reasons other than those caused by quality and manufacturing problems.

### **2.3. Regulatory changes**

Regulators have been asked to reflect on what they can do to support the implementation of the tools provided by the task force. Proposals have been made to reinforce the GMP guidelines, perhaps by including the requirement to assess supply chain resilience and shortages in the annual product quality review. This would allow inspections to assess the adequacy of the measures introduced. In addition, a proposal to include the topic within the scope of Site Master Files is also under consideration.

Previous ICH guidance provided opportunities for a more scientific and risk-based approach to assessing changes across the life cycle. However the main emphasis of these guidelines was on product development. As challenges in lifecycle management can lead to disruption in supply chain and medicine shortage, there is a need to focus more on the commercial manufacturing phase of the lifecycle to fully realise opportunities and benefits. The ICHQ12 guideline which is in development is expected to help ensure supply reliability by enabling strategic management of post-approval changes which could mitigate drug shortages related to manufacturing and quality issues.

### **2.4. Shortages continue to impact on patients and healthcare professionals**

Despite the work done to date, shortages continue to impact on patient care and patients are not well informed about shortages, their duration and resulting substitutions. In the community, patients are increasingly receiving different presentations and this can be due to shortages. Information provided to patients in these circumstances is generally sparse. In hospitals, the situation is similar and patients are generally not well informed about the medicines they are prescribed. They receive neither a copy of the prescription nor the package leaflet and may only obtain a copy of the discharge note when leaving hospital. It is not clear whether patients are informed at this stage of any medicine substitutions due to shortage. There is an urgent need to better inform patients about shortages and how it impacts on their care.

The extent of the problem of shortages was also revealed by the 2014 report of the European Association of Hospital Pharmacists (EAHP) on medicines shortages in European hospitals<sup>5</sup>. The report was the result of a survey of more than 600 hospital pharmacists in over 30 countries which showed that:

- 86% of hospital pharmacists reported that medicine shortages are a current problem in the hospital they work in, in terms of providing care to patients and/or operating the hospital pharmacy.
- 66% of respondents say that medicine shortages affect their hospital pharmacy on a daily or weekly basis.

- Antimicrobial agents, oncology products, emergency medicines, cardiovascular medicines and anaesthetic agents are the top affected categories.
- 75% of hospital pharmacists either agreed or strongly agreed with the statement "medicines shortages in my hospital are having a negative impact on patient care".
- 63% of hospital pharmacists estimate that the typical medicine shortage normally lasts for a number of weeks.

Reported impacts for patients included delayed or interrupted chemotherapy treatment, additional side effects, heightened *Clostridium difficile* risk and deterioration in their condition.

The picture is very similar in the community. A 2015 survey of community pharmacists undertaken by Pharmaceutical Group of the European Union (PGEU) showed that 73% of shortages lasted more than two months and 87% have potentially harmed patients. Pharmacists and other healthcare professionals usually lack information about why a shortage has occurred, and when the situation might improve, which means that they are unable to give assurance of future supply, creating uncertainty and anxiety for patients. Pharmacists spend an average of five hours each week dealing with medicine shortages. Most of this time is spent sourcing medicines from alternative suppliers. PGEU highlighted that more effort needs to be put into quantifying shortages as well as communicating shortages to healthcare professionals. The issue of communication should be carefully considered.

During discussions that took place after the presentations stakeholders agreed that information is lacking, however, there were reservations about the use of transparent shortage catalogues. The benefits of transparent communication to all stakeholders should be carefully weighed up against the potential for causing stockpiling and aggravations in shortages. All stakeholders agreed however that communication channels need to be improved to better exchange information on shortages. In addition there was agreement that in order to assess the full impact of shortages it is important to work with a common definition of shortages. Any definition would need to include a reference to a minimum period required to elapse before a supply disruption can be called a shortage.

## **2.5. Experiences by national competent authorities**

Currently national competent authorities have different measures and definitions in place to deal with shortages. In France for example, the French medicines agency (ANSM) defines a medicine shortage as the incapacity of a pharmacy/hospital to provide a medicine to a patient within 72 hours. A shortage can result from either a halt in the medicine's production or a disruption in the supply chain. To prevent medicine shortages France will introduce new measures to enforce Article 81 of Directive 2001/83 which is intended to ensure adequate supply of any given medicine to the market:

- Establishment of criticality of medicines

Medicines which are intended for the treatment of life-threatening or serious diseases for which no alternatives are available are classed as critical medicines. These are medicines for which disruption of treatment is life-threatening or irreversibly progressive, or without which the patient could be severely harmed. The list of critical medicines will be published and takes into account available alternatives, the market share of the medicine in France and the market shares of identified alternatives as well as weaknesses in the manufacturing process of the product e.g. absence of alternative manufacturing sites.

- Risk minimisation measures

When a shortage concerns a critical medicine the marketing authorisation holder must notify the national competent authority immediately and wholesalers should refrain from exporting the medicine in question. Marketing authorisation holders must also have in place call centres for pharmacists, hospital pharmacists and wholesalers. Consideration should be given to including the critical list of medicines in the site master file.

Small countries such as Ireland are particularly vulnerable to shortages because of their small market size. Supply is therefore very sensitive to appropriate forecasting by the marketing authorisation holder. Shortages can result from company mergers or divestments of products from one company to another. Shortages can follow re-evaluation of a product's profitability due to product packaging and livery changes. Because of the small size of the market, low revenue is often cited by marketing authorisation holders as a reason for discontinuation of a medicine. Shortages have both a patient impact and resource impact. In Ireland there is no single body responsible for shortages. The Health Products Regulatory Agency (HPRA) and the Health Service Executive work together in many cases. Current approaches to managing shortages include the granting of a temporary authorisation for a batch of a product known as a 'batch specific request'. Just as for bigger Member States the importance of good communication was highlighted; however, the flow of information is usually quick. A full list of essential medicines is not in place. A draft template for notification and analysis of the shortage has been drafted.

### **3. Conclusions and way forward**

The stakeholder meeting reviewed the progress made since the workshop in 2013 and discussed the way forward. Although the work done so far to deal with shortages is encouraging, shortages continue to impact patient care and further effort is needed to more proactively avert shortages and reduce their impact.

Following the workshop, the Agency will seek to involve stakeholders to collaborate in order to address the following recommendations made during the workshop:

- There is a need for a harmonised definition of a medicine shortage and a common understanding of the evolution of potential supply disruptions. It is important to identify at what point a manufacturing or quality issue becomes likely to lead to a meaningful disruption as well as when it should trigger a report.
- A harmonised reporting template was considered too rigid by regulators who instead preferred to agree on common trigger points for notification as well as harmonised data requirements across the EU. This would allow information to be gathered in a consistent manner and to facilitate the coordination between assessing competent authorities.
- Considering the complexity of the supply chain, an improved flow of information is needed. Managing a disruption in supply can be complex and time-pressured and the mechanism for notifying disruptions to competent authorities should be transparent, simple and consistent.
- In this respect, a single point of contact at national competent authorities and the Agency should be designated. This will facilitate a coordinated and standardised approach for assessing the impact on public health and for planning potential communications. Stakeholders shared the view that a communication network similar to the rapid alert network should be set up.

- The tools developed by industry now need to be implemented and their impact should be measured. Companies need to be asked to put in enhanced measures to prevent shortages and to maintain supply for critical medicines. The evaluation of the risk of shortages needs to be incorporated in the assessment by the NCA inspections program. Industry should consider the value of stress tests to evaluate effectiveness of measures in place to prevent shortages.
- Common points and differences in the way international regulators deal with shortages should be further explored. The Agency should continue their interaction with international regulators to exchange and compare experiences and best practices.
- The potential to involve all relevant parties in the notification of shortages to the national competent authorities should be explored. This includes the supplier's direct supply channel, logistics providers, wholesalers, distributors, pharmacies and other health care providers. In particular, the role of patients should be further explored.
- Further discussions to take place across the network and with the European Commission on the possibility of updates to the Annual Product Quality Review and to the Site Master File guidelines.

The Agency will update its implementation plan with these recommendations. It will seek to re-convene the virtual working group and ask the inter-association taskforce to focus on implementing its guidance. A follow-up workshop will be convened in 2 years' time involving a wider range of stakeholders.

Disruption of the supply chain leading to shortages represents a significant risk to public health. The workshop concluded that it is only adoption of a collaborative approach between the various stakeholders and regulators, combined with a better business continuity planning by industry that will help to prevent shortages. In the context of a complex global supply chain the need for good communication between manufacturers and authorities and vice versa is key in this objective.

## 4. References

1. European Medicines Agency. Reflection paper on medicinal product supply shortages caused by manufacturing/Good Manufacturing Practice Compliance problems. 2012. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2012/11/WC500135113.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/11/WC500135113.pdf).
2. The Association of the European Self-Medication Industry, The European Bioinformatics Institute and the Plasma Protein Therapeutics Association. Quality and Manufacturing Driven Supply Disruptions Industry Communication Principles to Authorities. 2012. [http://www.efpia.eu/uploads/Industry\\_Communication\\_Principles\\_Principles\\_Dec2014\\_Final\\_v1.pdf](http://www.efpia.eu/uploads/Industry_Communication_Principles_Principles_Dec2014_Final_v1.pdf)
3. International Society for Pharmaceutical Engineering. Drug Shortage Prevention Plan 2014 and Drug Shortage Assessment and Prevention Tool 2015. <http://www.ispe.org/drug-shortages-initiative/survey-plan-tool>
4. Parenteral Drug Association. PDA Technical Report No. 68 Risk-Based Approach for Prevention and Management of Drug Shortages. 2014.
5. European Association of Hospital Pharmacists. 2014 survey of medicines shortages in European hospitals. 2014.

## 5. Annex I: Shortage Workshop 2015 Evaluation Report

On 9 October 2015, representatives of national competent authorities, pharmaceutical industry and healthcare/patients associations met to continue the discussion in relation to product shortages started in October 2013.

Each attendee was asked to complete an evaluation form at the end of the day. What follows is the analysis of responses received.

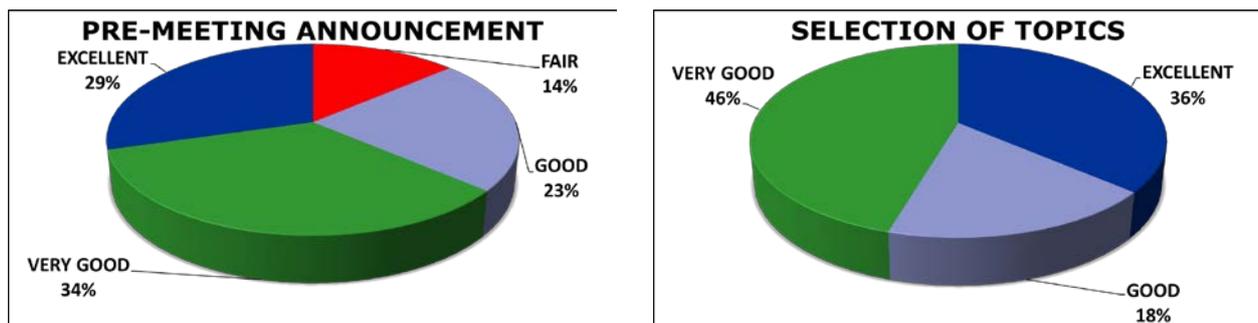
### 5.1. Sessions A and B - Attendees and organisation

A total of 59 representatives attended the workshop with an additional 24 following the discussion online.

The audience was a heterogeneous mix of national competent authority (NCA), industry, healthcare professionals (HP) and patient-groups representatives.

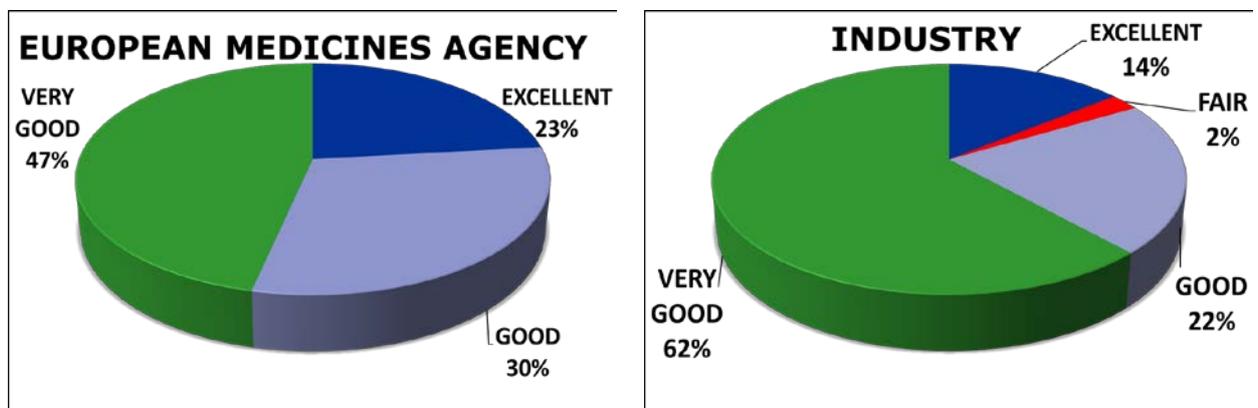
Attendees showed general satisfaction with pre-meeting announcements, topics selected and discussed.

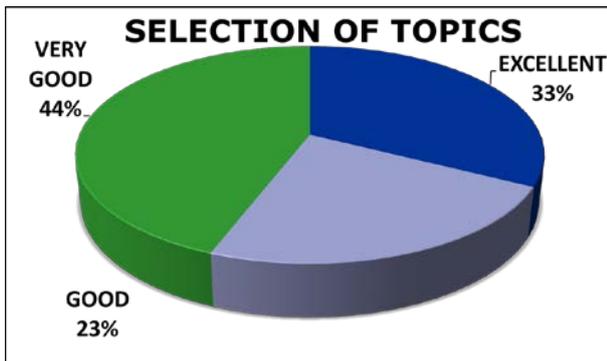
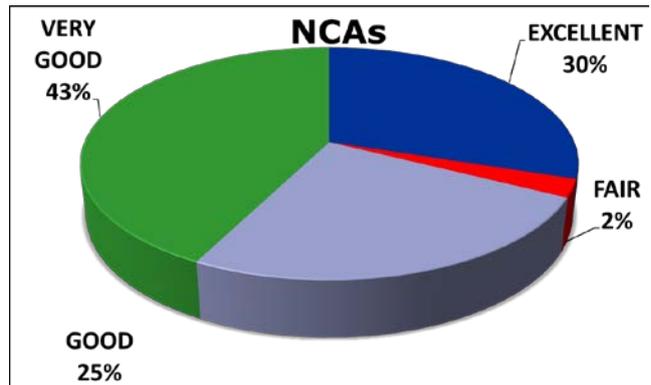
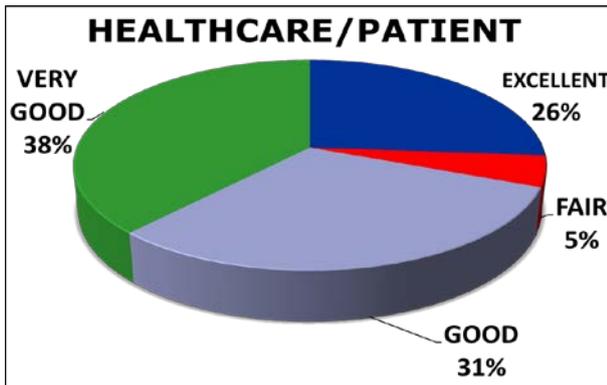
The main criticism was in relation to delays in providing the agenda and presentation materials.



### 5.2. Session C – Speakers

In general, attendees gave a positive rating for all the presentations. However, time constraint was noted by the audience.





### 5.3. Session 3 - Workshop

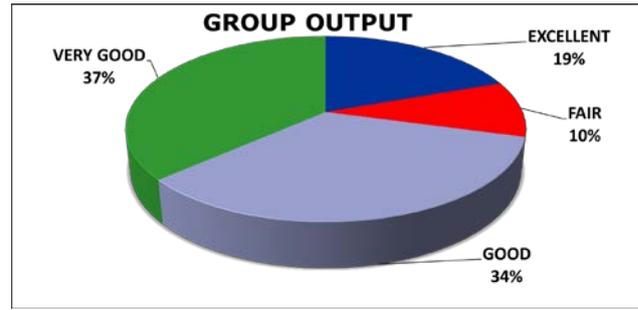
The audience was divided in four groups and was asked to perform a brainstorming exercise on the following discussion points:

- Best practice with respect to shortages and meaningful supply disruption and how best practice can be implemented.
- How can we define a “drug shortage”? How can a shortage be measured?
- Communication of shortages.
- Can shortage best practices be tailored to other areas of the supply chain (e.g. good distribution practice)?

The approach of having mixed groups (patient, healthcare professional, industry and regulator) in the work streams was welcome by the attendees. The open discussion and the cross engagement of representatives from the different groups was appreciated.

The survey results were generally good. However, 10% of the audience were not satisfied with the output of their group. Comments in relation to the lack of time (30 minutes session for a large topic), rooms not being suitable and lack of clear conclusions were reported.

The need to have the list of topics for discussion at an earlier stage in a pre-mail was recognised.



#### 5.4. Session 4 – NCAs only

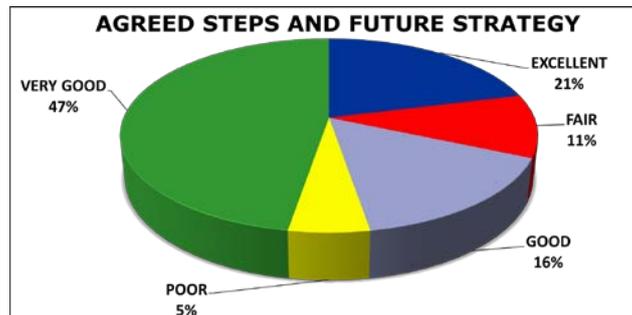
A recap of the main points raised during session 3 was performed.

The following next steps were agreed:

- Develop trust to ensure best practice implementation
- Define “shortage” and how to measure it

The survey demonstrated that 16% of the NCA representatives considered as “fair/poor” the recap session. This reflected the concerns in relation to inadequate details regarding next steps. However the majority of attendees felt that the meeting did clarify next steps.

Comments received highlight that there is the need to have a clear deadline or a timeframe for future actions and this was not achieved during the meeting.



#### 5.5. Comments and suggestions

The audience was generally satisfied with the one day workshop format.

The opportunity for open interaction between representatives of industry, healthcare professional and regulators was welcome.

The atmosphere was relaxed and it was easy to engage in discussion with all the representatives.

The importance of having face to face discussion was recognised.

There were suggestions to have more interactions to harmonise working strategies and improving relationship across Europe.

The organisation of the workshop was judged excellent, even if disappointment was raised in relation to the timing of providing agenda and meeting materials.

Publication of position papers and guidelines from the EMA is welcome.

Attendees would like to discuss the following topics:

1. Development of common approach to management and reporting of shortages.
2. Identification of regulatory initiatives that may impact/provoke shortages.
3. Shortages of vaccines.
4. How should MAHs communicate with Member States when shortage impacts different Member States.
5. Development of "list of products/APIs" in recurrent shortage.
6. Implementation of best practices in industry.