Pharmaceutical Supply Chains I

IMPROVED INFLOWS TO CURB MEDICINES SHORTAGES

Lisbon - April, 26, 2017

European Industrial Pharmacists Group
Groupement des Pharmaciens de l'Industrie en Europe

Shortages of Medicines Originating from Manufacturing

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Single Points of Contact
Good Manufacturing Practices
Surveillance and Monitoring
Good Distribution Practices
SUPPLY CHAIN SECURITY TOOLKIT for Medical Products
Track and Trace System
Good Import/ Export Practices
Internet Sales
Clinical and Retail Pharmacy Practices
Detection Technology
Product Security
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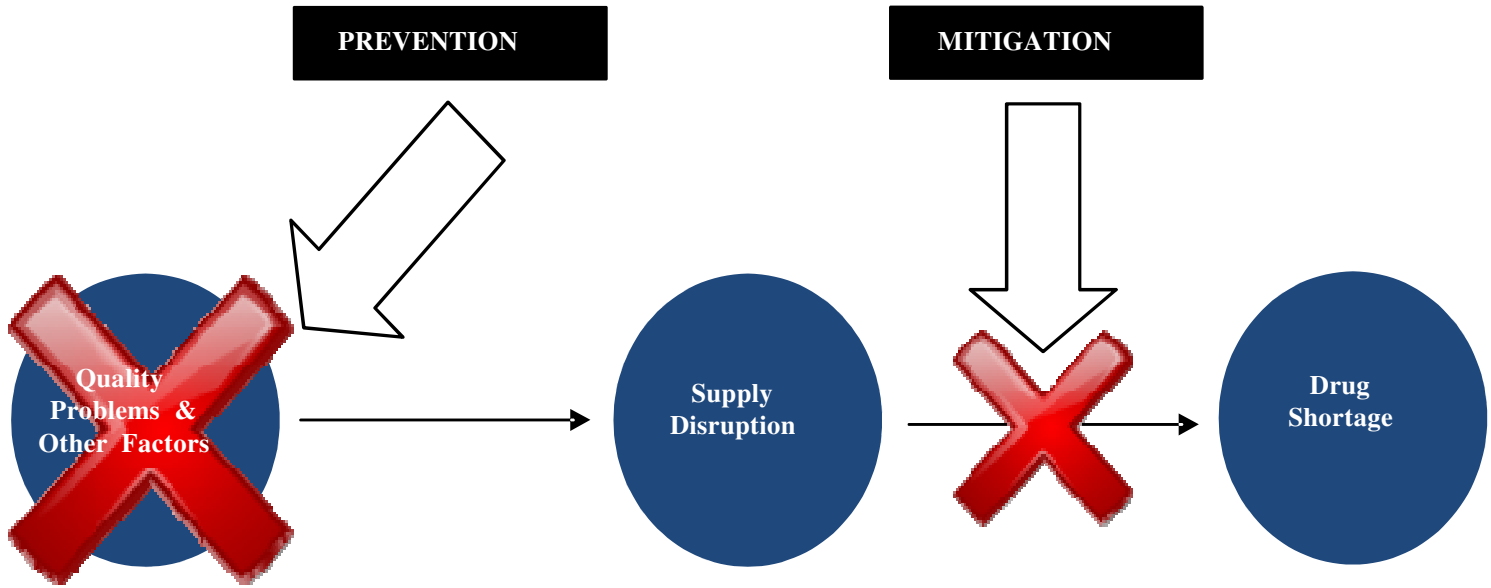
"Developing a proactive approach to the prevention of medicines shortages due to manufacturing and quality problems"

Report from a stakeholder meeting at the European Medicines Agency - 9 October 2015

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.

Mitigation *activities are directed at* **preventing supply disruptions from turning into actual shortages**. *Long-term* ***Prevention*** *strategies are intended to address the* ***underlying causes of shortages to prevent supply disruptions from occurring in the first place.***



Goal #1	**STRENGTHEN MITIGATION RESPONSE** Improve and streamline mitigation activities once the Agency is notified of a supply disruption or shortage.
Goal #2	**DEVELOP LONG-TERM PREVENTION STRATEGIES.** Develop prevention strategies to address the underlying causes of production disruptions to prevent drug shortages.

MITIGATION EXAMPLE

When particulate matter (including glass and metal particles) was found in an injectable drug product that was medically necessary and vulnerable to shortage, FDA exercised discretion to allow distribution of the product along with a letter, included in the drug's packaging, warning health care professionals to use a filter when administering the drug. The exercise of discretion was temporary, and was conditioned on the manufacturer's ability to demonstrate to FDA that the filter did not affect the way the drug works and could successfully remove the particulate. FDA also worked with the manufacturer while the manufacturer identified and addressed the root cause of the problem, so that it could resume producing a drug product that did not need the work-around involving the filter.

In contrast, a drug that is contaminated with bacteria or fungi presents a more extreme risk to patients, one that cannot be mitigated through a work-around such as the one described above. In such cases, the manufacturer must correct the conditions leading to the contamination before the product is safe for use, even if correcting the conditions ultimately leads to a shortage.

Each situation must be carefully evaluated to determine the public health impact, keeping in mind that a given action may have unintended, and potentially long-term, consequences.

Le Groupe de travail Approvisionnement et Economie de la GSASA informe

Ruptures de stock de médicaments: un véritable défi pour le pharmacien d'hôpital

*Herbert Plagge, Cornelia Desax, Richard Egger**

Les ruptures de stocks touchant la chaîne d'approvisionnement de médicaments existent déjà depuis longtemps en Suisse. Elles posent problème au personnel soignant, aux pharmaciens et enfin aux patients. En effet, la non-

dernières ann
calade au co
Désormais ce

Retraits, ruptures, rappels: ras le bol ...

André Pannatier

Schweizerischer Verein der Amts- und Spitalapotheker
Association suisse des pharmaciens de l'administration et des hôpitaux
Associazione svizzera dei farmacisti dell'amministrazione e degli ospedali
Swiss Association of Public Health Administration and Hospital Pharmacists

GSASA

Empfehlungen zum Umgang mit Lieferengp

Die Arbeitsgruppe Ökonomie und Versorgung der GSASA wurde beauftragt, Empfehlungen und Anliegen seitens der Spitalapotheke

Maladies transmissibles

Approvisionnement en vaccins en Suisse : analyse de la situation et prochaines

L'Office fédéral de la santé publique p
laque année le Plan de vaccination suisse. Mais c

Bloc-notes

Troublantes pénuries de médicaments

On est au 21e siècle, les magasins regorgent de superflu, le frivole envahit les étals, le luxe

Pour dire les choses résulterait de manipul

intermédiaires qui font fortune en achetant en masse (ce qui crée la pénurie) pour revendre

est

Datum: 20.06.2015
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Medientyp: Tages- und Wochenpresse
Auflage: 39828
Erscheinungsweise: 6x wöchentlich
Themen-Nr.: 526.001
Abo-Nr.: 526001
Seite: 3
Fläche: 75228 mm²

VACCINS *Des préparations essentielles en pédiatrie pour lutter contre la diphtérie, la polio ou la coqueluche ne sont plus disponibles. Les praticiens dénoncent un manque de prévision.*

Rupture de stock au pays de la pharma

PIERRE-ANDRÉ SIEBER

«Rupture de stock des vaccins.» L'alerte est tombée il y a peu dans les boîtes mail des pharmaciens suisses. Du

mi-juillet.

Ersatz pas satisfaisant

Le marque n'épargne pas la vacci-

au-dessous des normes fixées.»

Processus exagérément contrai-
gnant lorsque l'on sait que le temps né-
cessaire à la production et à la vérifica-

European initiatives - Recent History and Background

However, the *European Medicines 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. 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.

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 noncompliance/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.

In October 2015, the Agency convened a second stakeholder meeting bringing together national competent authorities, industry, 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.

Break-out individual sessions:

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

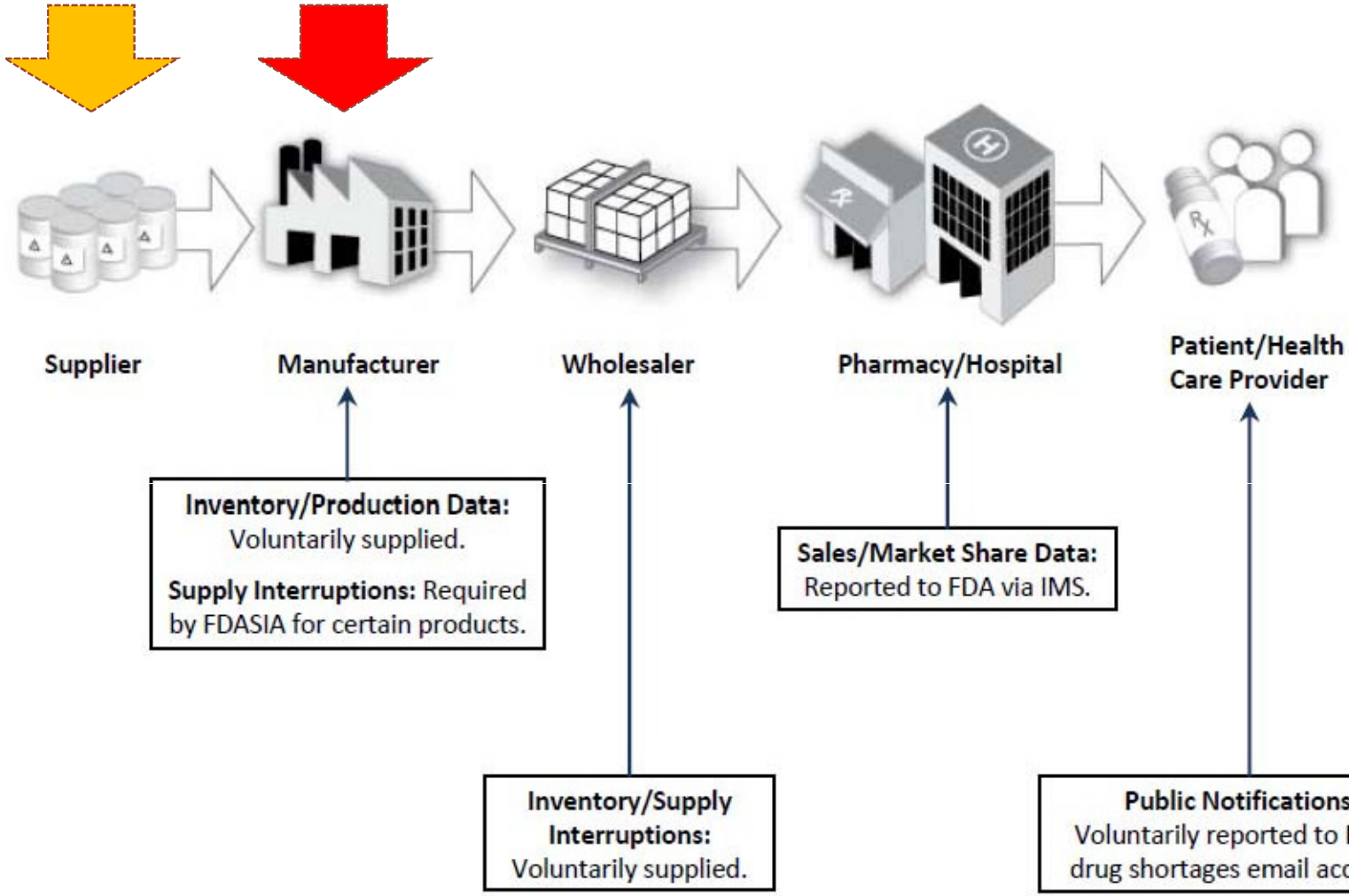
Feedback of the break-out sessions would be used to update the shortage implementation plan. The third part with representatives from national competent authorities was used to agree on a common approach amongst regulators.

PDA and ISPE worked together "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. 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 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. 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.

Supply Chain Information Sources



However, although extremely useful, the information sources shown in the previous slide produce only part of the picture. For example, key aspects of drug manufacture and distribution are not transparent, such as production schedules, distribution of production volume across various contract manufacturing facilities, the amount of inventory stored by a manufacturer, and wholesaler and pharmacy/hospital supply and purchasing practices. Additionally, the role that other sources of products (e.g., gray market distribution, compounding, unapproved drugs) play in contributing to shortages or in the reactions to shortages is not clearly understood.

Criteria for classification of critical medicinal products

GMP non-compliance/quality defects may lead to shortage of a product, if it is decided not to release a batch or even to withdraw batches from the market; this is good precautionary practice but there might be situations where withdrawing a product or not releasing it might do more harm to a patient than allowing a product to remain or to be released on the market.

When defining a product as critical,
two criteria are of importance:

1. THERAPEUTIC USE

2. AVAILABILITY OF ALTERNATIVES

Therapeutic use

The medicinal product is an integral part of the treatment for a disease, which is life-threatening or irreversibly progressive, or without which the patient could be severely harmed. This could be in acute situations (e.g. emergency situations), or chronic situations/maintenance of stable conditions, or disease with a fatal outcome where the product has been shown to affect the progression of the disease or survival.

Availability of alternatives

Even if the product would be used in the situation defined above, it would not be classified as being critical in case appropriate alternatives are available. These could be:

- Alternative manufacturing site for the same product;

bottle neck: manufacturing capacity and technical and regulatory times to switch.

- Different strength/formulations of the same product;

bottle neck: need for formulations suitable for use in special populations.

- Alternative dosing (lower dose/temporary break from drug treatment) or limiting the use to high risk patients could be explored;

bottle neck: this might depend on the expected duration.

- Generics;

bottle neck: the availability and volume should be checked.

- Other products in the same class or even other classes;

bottle neck: adverse events.

Points to consider for the overall assessment of a supply shortage of a medicinal product due to GMP Noncompliance /quality defects

Product and manufacturing related question

a. Which batches, pharmaceutical forms, strengths, pack sizes are affected by the supply problem?
b. Which countries are experiencing supply interruption? I
c. Is it likely that the supply problem will affect other countries in the near future?
d. Is a stock-out, or near stock-out situation likely to occur? If so, in which countries?
e. Provide a technical report of the problems in the manufacturing or quality area that means that has given rise to the possibility of a shortage. The Manufacturing Authorization Holder should be asked to provide analytical data and should discuss the relevance of the data. What is the root cause of the supply interruption and where in the manufacturing process does it occur?
f. What preventive and/or corrective actions has the company taken to avoid and/or resolve the deviation and the shortage?
g. Member State to countries where shortage is evident? If so, how would this be handled?
h. Have all alternatives of improving the supply chain been explored? E.g. modification of manufacturing process, use of alternate manufacturers, etc.
i. What is the stock situation for other strengths or formulations of the medicinal product that could compensation for the supply interruption?

Points to consider for the overall assessment of a supply shortage of a medicinal product due to GMP Noncompliance /quality defects

Product and manufacturing related question

j. What is the current stock situation/member state? Are there any buffer stocks at distributor or hospital sites? Forecasted demand rates and estimated stock out dates should be provided. Discussion on the feasibility of stock rotation between member states to cover and any other measure to prevent the shortage should be requested.

k. What is the estimated lead-time before the product reaches out of stock level? Provide lead times and a timetable for (a) manufacture and supply utilizing the batches in question and (b) manufacture and supply utilizing new batches.

l. Considering the nature of the defect, what is the level of risk of the use of a defected product from the quality point of view? What is the threshold beyond which the quality defect has harmful effect on the patient and clinical use would deem inappropriate?

m. Is it possible to import the medicinal product (re-packging and re-labelling) from other EU member state to countries where shortage is evident? If so, how would this be handled?

n. Have all alternatives of improving the supply chain been explored? E.g. modification of manufacturing process, use of alternate manufacturers, etc.

o. What is the stock situation for other strengths or formulations of the medicinal product that could compensation for the supply interruption?

Chapter 8 EU Guidelines (Vol. 4)
Complaints, Quality Defects and Product Recalls

8.27 It should also be considered whether the proposed recall action may affect different markets in different ways, and if this is the case, appropriate market-specific risk-reducing actions should be developed and discussed with the concerned competent authorities. The risk of shortage of an essential medicinal product which has no authorised alternative should be considered before deciding on a risk-reducing action such as a recall. Any decisions not to execute a risk-reducing action which would otherwise be required should be agreed with the competent authority in advance.

Identification of Risk Indicators for Shortages Manufacturing and Quality

Product Identity and origin

Name

Active substance

Pharmaceutical Form

□ *Chemical*
□ *Sterile*
□ *Biological*

Application number: EMEA/ / /

Authorisation number: EU/ /

Supply Chain Risk Factor Evaluation

1 There is only a single manufacturer of the API registered

2 There is only a single manufacturer of Finished Product registered

3 Location of the Manufacturing Site(s) cause any concern? This may be based on a general concern that there is a potential for future disruption in the supply due to the geographical location of the manufacturing facility, or source of plant or animal materials

4 One or more manufacturing sites have a marginal level of GMP compliance or are subject to increased inspection surveillance. (link to EudraGMDP (1) and potentially risk based classification) This should be based on what is in the marketing authorisation application and checking EUDRAGMP during the assessment and ideally liaising with the inspectorate.

(1) Directives 2004/27/EC on human medicinal products and 2004/28/EC on veterinary medicinal products introduce the legal framework for the Community database.

The concept of a European Inspections database is included in the above specified legislation to provide EEA National Competent Authorities and the European Medicines Agency (EMA) with an overview of the status of pharmaceutical manufacturers. The legislation provides for an electronic tool containing complete information on all pharmaceutical manufacturers. This includes information on Manufacturing and Importation Authorisations (MIA) and Good Manufacturing Practice (GMP) Certificates for authorised sites in the EEA and information on GMP certificates for manufacturers in third countries.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000159.jsp

Supply Chain Risk Factor Evaluation

5 There is a high product concentration at the finished product manufacturing site

6 End to End Manufacturing process has long lead/holding times and/or extended supply chain

7 Manufacturing methods are complex, with capacity bottle necks in production

8 The manufacturer has had previous problems with quality defects and/or recalls

9 The manufacturer has had previous problems with supply

10 The medicinal product would meet the criteria of critical Based on classification criteria for critical medicinal product agreed by Committee for Medicinal Products for Human Use (CHMP) http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000094.jsp

11 design/device feature of the medicinal product could potentially prohibit switching patients.

EUDRA GMPD DATABASE (1)

Compliance with Good Manufacturing Practice

A certificate of Good Manufacturing Practice (GMP) is issued to a manufacturer by the national competent authority that carried out an inspection if the outcome of the inspection confirms that the manufacturer complies with the principles of Good Manufacturing Practice, as provided by European Union legislation. If the outcome of the inspection is that the manufacturer does not comply a statement of non-compliance may be entered into EudraGMDP. Certificates and statements of non-compliance may be issued to manufacturers of medicinal products and manufacturers of active substances located inside and outside of the European Union.

Manufacturing and Importation Authorisation

Manufacture of medicinal products in the EU or importation from a third country is subject to the holding of a Manufacturing and Importation Authorisation. The National Competent Authority of the Member State in which the manufacturer or importer operates issues these authorisations.

EUDRA GMPD DATABASE (2)

Compliance with Good Distribution Practice

A certificate of Good Distribution Practice (GDP) is issued to a wholesale distributor by the national competent authority that carried out an inspection if the outcome of the inspection confirms that the wholesale distributor complies with Good Distribution Practice, as provided by European Union legislation. If the outcome of the inspection is that the wholesale Distributor does not comply a statement of non-compliance may be entered into EudraGMDP. GDP certificates and statements of non-compliance may be issued to wholesale distributors of medicinal products and distributors of active substances.

Wholesale Distribution Authorisation

The wholesale distribution of medicinal products is subject to the holding of a Wholesale Distribution Authorisation. The National Competent Authority of the Member State in which the wholesale distributor operates these authorisations.

Registration of Active Substance manufacturers, Importers and Distributors

Manufacturers, importers and distributors of active substances are required to register their activities with the National Competent Authority of the Member State in which they operate.

Manufacturing and Quality constraints

- *RELIABILITY OF SUPPLIERS OF CRITICAL STARTING MATERIALS (mainly MANUFACTURER OF API'S outside Europe)*
- *DISCONTINUATIONS . (sometimes OLDER DRUGS ARE DISCONTINUED IN FAVOR OF NEWER, MORE PROFITABLE DRUGS)**
- *JUST-IN-TIME INVENTORY PRACTICES THAT RESULT IN MINIMAL PRODUCT INVENTORY BEING ON HAND AT ANY GIVEN TIME*
- *GLOBALIZATION OF MANUFACTURER*
- *CONCENTRATION OF PRODUCTION SITES*
- *PRODUCTION ISSUES (see next slides)*
- *COMPLEXITY OF THE PRODUCTS*
- *INCREASING REGULATORY REQUIREMENTS*
- *SLOW INCREASE OF PRODUCTION CAPACITY*

BUILDING REDUNDANCY, HOLDING SPARE CAPACITY, AND INCREASING INVENTORY LEVELS COULD LOWER THE RISKS OF SHORTAGES.

*With fewer firms making older sterile injectable drugs, there are a limited number of production lines that can make these drugs. The raw material suppliers that the firms use are also limited in the amount they can make due to capacity issues at their facilities. This small number of manufacturers and limited production capacity for older sterile injectables, combined with the long lead times and complexity of the manufacturing process for injectable drugs, results in these drugs being vulnerable to shortage. When one company has a problem or discontinues, it is difficult for the remaining firms to increase production quickly and a shortage occurs.

Guaranteed utilization orders

Many companies think that guaranteed utilization orders (a commitment to order a specific amount annually) to manufacture lower-margin, lower volume products, could reduce shortages of those products, especially those without predictable demand. Guaranteed orders could provide the proper incentives to the companies in order to invest in backup facilities or new manufacturing lines as a way to protect against potential shortages.

Regulatory expectations and legacy products

Increasing regulatory expectations for legacy products is one of the obstacle to prevent shortages. Unfortunately many companies not want to either incur the costs of submitting new or supplemental filings or to risk current regulatory scrutiny, and associated delays, for taking actions required to upgrade a facility or the equipment. Investments in facilities that manufacture legacy products are lower due to challenges in assuring regulatory compliance of legacy products for which development histories are often not available, either because of multiple company acquisitions or because the products were developed many years ago. The time required to get an application approved also contributed to their decisions not to invest in the facilities or equipment that could prevent a shortage.

Regulatory expectations and legacy products

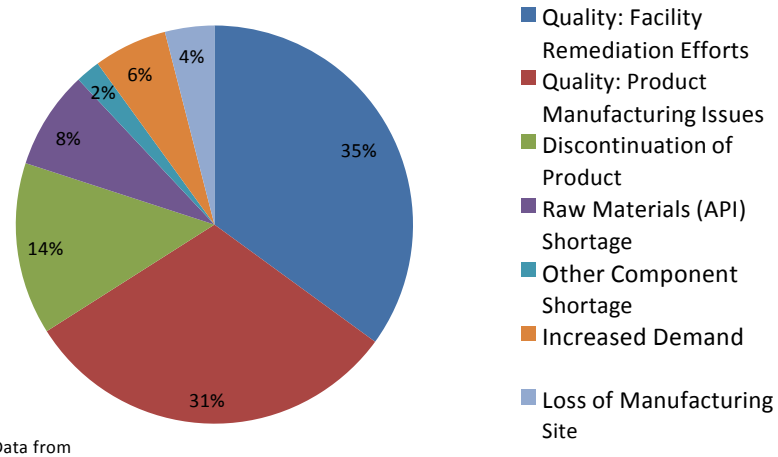
Shortages of legacy products can be also connected with analytic methods used for detecting impurities for which the revalidation requests high costs associated to concerns over the potential rejection of a re submitted regulatory application. It's a big challenge to improve analytical methods when the development histories for legacy products are not as robust as those of more recently developed products.

Some form of regulatory discretion and increased collaboration with the involved Authorities would enable to reduce the risk of supplies interruption by building more resilient supply chains (including upgrading facilities, building new manufacturing lines, or adding new contract manufacturers in a more efficient manner), in particular for legacy products.

In 2012, for example, based on information collected from manufacturers, FDA determined that the majority of production disruptions (66%) resulted from either

(1) efforts to address product-specific quality failures (31%, labeled Quality: Manufacturing Issues)
(2) broader efforts to remediate or improve a problematic manufacturing facility (35%, labeled Quality: Remediation Efforts).

Quality or manufacturing concerns can involve compromised sterility, such as roof leakage; mold in manufacturing areas; or unsterilized vials or containers to hold the product—issues that could pose extreme safety risks to patients.



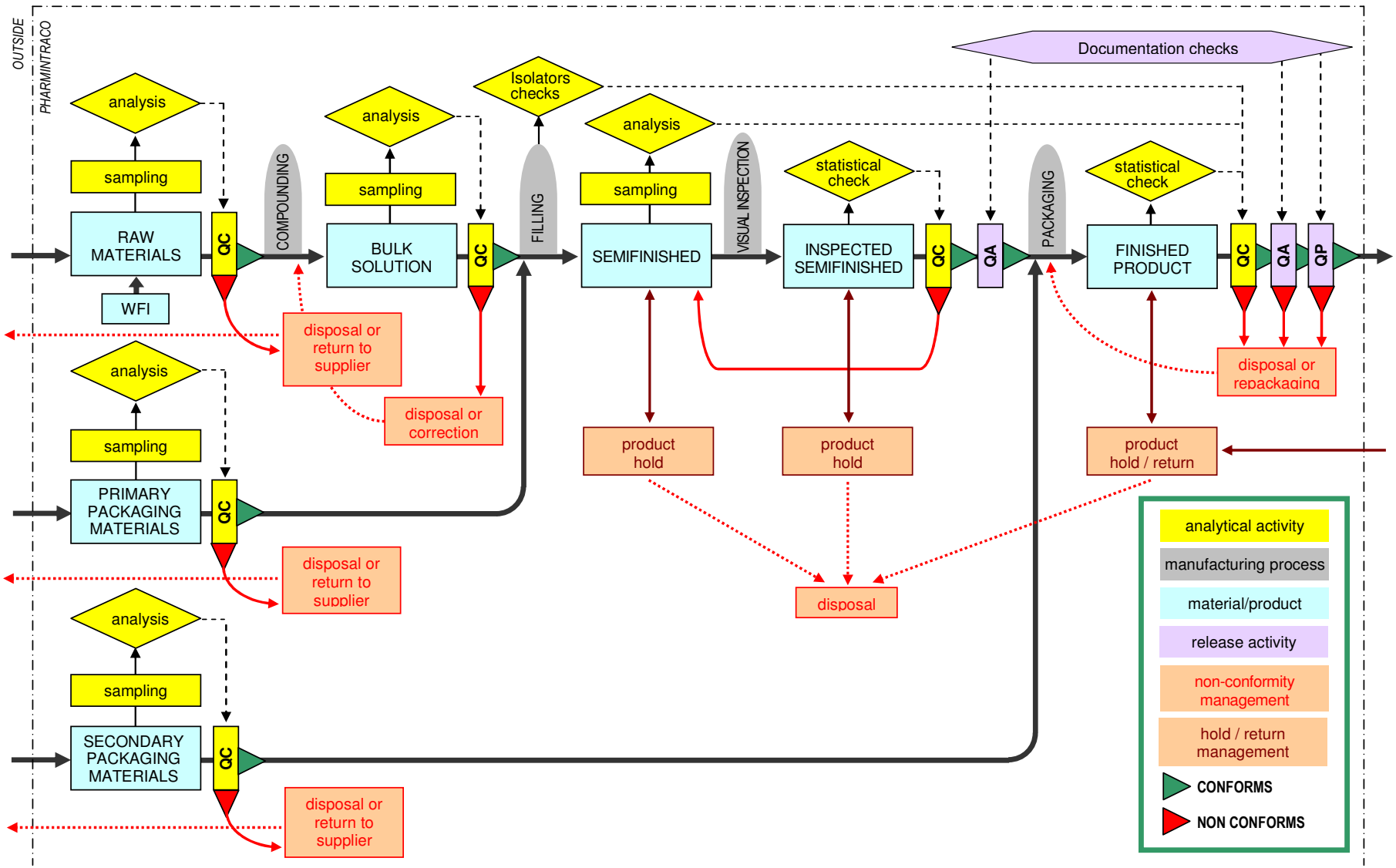
Source: Data from FDA's internal drug and biologics shortages databases.

The majority of the shortages, more than 72 percent, were in the sterile injectable category, and the affected product categories or therapeutic classes ranged from anti-infective and anesthetic drugs to cardiovascular and oncology treatments.

The International Society for Pharmaceutical Engineering (ISPE) conducted a survey of its membership and found that compliance, together with manufacturing and product quality issues, represented the single most important factor leading to drug shortages.

There are many shortages that are not influenced by correlations with quality and manufacturing factors, like: market uncertainties and product margins; supply chain network design; demand forecasting; relationships between manufacturers and key stakeholders, including purchasing organizations and regulators.

Identification of Critical Steps for Shortages in a Manufacturing Process
WORST CASE SCENARIO – ASEPTIC MANUFACTURING



Identification of Risk Indicators for Shortages - Manufacturing and Quality

Manufacturing and Control - Main Causes of potential Shortages

- ✓Unexpected shortages of Starting Materials, Intermediates, Auxiliary Materials (including laboratories supply and spare parts)
- ✓Starting materials (API, Excipients, Primary and Secondary Packaging Materials, Printed Packaging Materials) affected by unexpected defects of non compliance.
- ✓Intermediates produced far away from final product assembling.
- ✓Contaminations, impurities happen, due to significant quality assurance issues during manufacturing steps.
- ✓Occurrence of a quality defect despite all measures were taken according to quality standards.
- ✓Unforeseen results of environmental monitoring in routine manufacturing (especially in the aseptic process manufacturing) but also in the periodic process simulation trials (media fill performed in the shutdown period)

✓Manufacturing capacity overload

✓Sudden or unexpected failure of instruments or systems (time of reaction frequently linked with maintenance and repair interventions involving external supplier and spare parts procurement)

✓Unexpected lack of staff

✓Delay in the time of release

✓Failure of control in process or cleaning checks

✓Delay of quality Procedures/Processes having an impact on the time of the release (Deviation management - root cause investigation and finding, CAPA/RAC implementation, risk assessment development, extraordinary analysis, ….; Change Control management; Complaints management; …)

✓Carriers delay affecting the shipment of the goods

✓Delays occurred in developing and transferring the analytical methods needed to support the transfer of a legacy product (a drug typically developed 10 to 20 years ago) to a new manufacturing site

✓Violations as a result of the company's final product contract manufacturing site not following certain cGMP regulations.

Strategies for shortages risk reduction

Business continuity planning

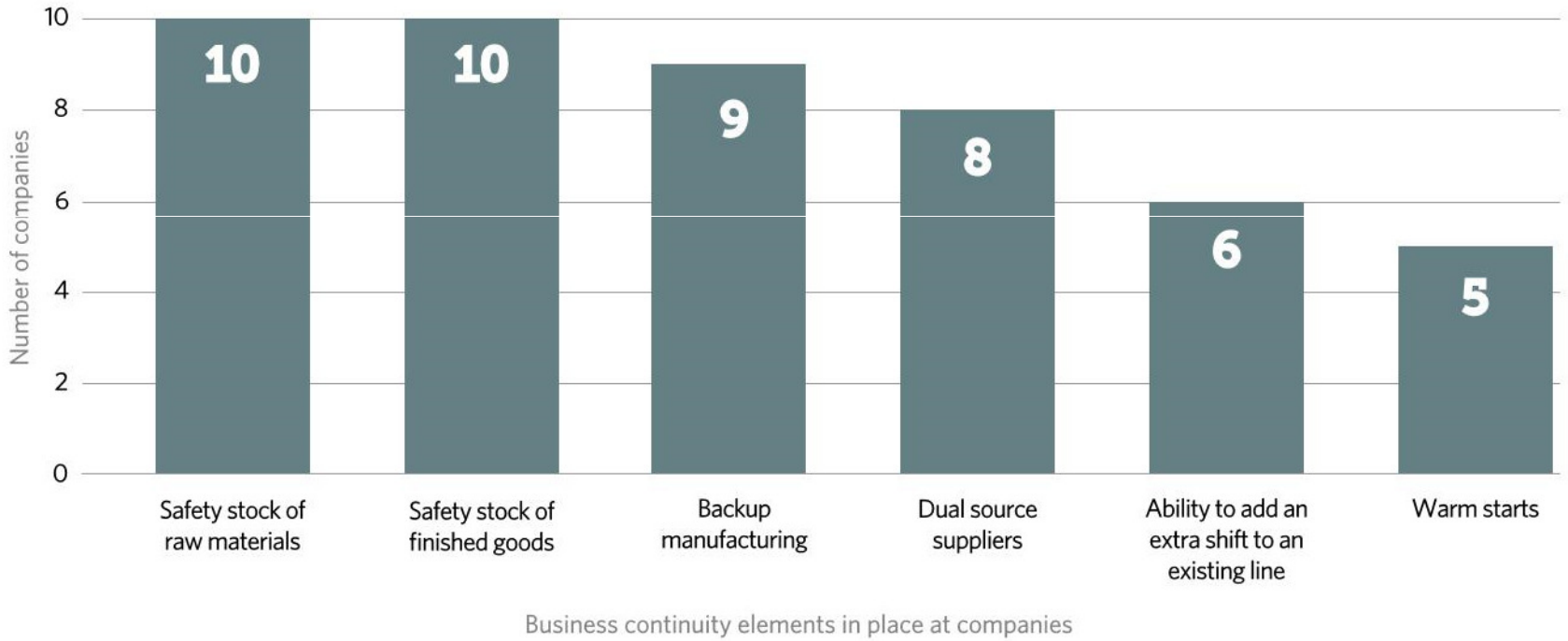
Decisions and plans that drive the ways companies design and structure their manufacturing networks to reduce the risk of supply interruptions by identifying backup manufacturing facilities, building new manufacturing lines within existing facilities, and/or establishing dual-source suppliers to react quickly to sudden, unexpected spikes in demand.

Supply chain management

Capability of a company's inventory management, demand planning, and forecasting accuracy to enhance the organization's ability to proactively avoid a supply interruption by aligning the predicted demand volumes with the material inventory levels needed.

Business Continuity Elements

Reviewed gaps across the supply chain management processes allow to identify areas for prevention of future shortages. There are some business continuity elements involved in protecting against a sudden and unexpected demand for a product.



Safety stock of raw materials

Maintain buffer or extra stocks of raw materials needed to meet rapid and unexpected increases in product demand

Safety stock of intermediates and finished products

Store backup inventory of finished products in order to protect against unexpected product demand. Maintaining backup inventory of key drug intermediates is an additional strategy

Backup internal and external manufacturing facilities

Additional facilities in place to manufacture same finished products. Backup manufacturing for products that required dedicated facilities is mainly limited by the fact that the expected rate of return is low due to the reduced sales volume anticipated for the products

Dual-source suppliers

Second source suppliers in place to provide the components needed to manufacture finished products. Despite this safeguard in place there are residual risks related to supply interruptions due to quality issues

Ability to add a shift to an existing manufacturing line

Processes in place to swap the manufacturing of one product with one at risk of a shortage. This strategy risk to create a shortage for the product that was replaced

Warm starts

Ramp up operations at a contract manufacturer to help meet unexpected and sudden surges in demand. The resources needed required significant investment and for that reason is limited to products having relevant annual sales or percentage of market shares.

Points of reflection

Some product classes, such as antibiotics, hormones, and/or cytotoxic drugs, may require dedicated manufacturing facilities, an added challenge for these products. Manufacturing facilities requiring segregated, self-contained, or specialized lines prevented the establishment of redundant capacity due to the investments that would be required for products where demand might not be stable on an annual basis and might have low margins.

The existence of multiple suppliers does not negate the potential of a shortage, since each manufacturer could experience difficulties in ramping up operations when a competitor withdrew from the market. The new paradigm has shifted from dual sourcing and backup manufacturing options for products to a network with limited sourcing and fewer manufacturing options when products went off patent.

Strengthening quality and the development and implementation of systems that proactively identify, measure, and monitor risks across the manufacturer's overall supply chain are the main points to take in proper consideration. This includes cGMP compliance risks as well as issues that may develop when there are no robust development and/or manufacturing processes in place. Manufacturers should be diligent in selecting suppliers and, when necessary, partner with them to help improve their quality systems.

Some Strategic Questions to answer

WHAT ARE THE FIVE MAIN TOPICS OF YOUR BUSINESS CONTINUITY PLAN?

WHAT ARE THE CONNECTION AND THE KEY FACTORS BETWEEN: PRODUCTION PLAN - INVENTORY PLAN - SALES PLAN - FINANCIAL PLAN – SALES FORECAST PERIODIC REVIEW?

WHAT ELEMENTS ARE CONSIDERED FOR SOURCING FROM SUPPLIERS? CRITICAL MATERIAL, HIGH-VOLUME,….?

ARE CONTRACT MANUFACTURERS AND CRITICAL SUPPLIERS INVOLVED IN PRODUCTION PLANNING?

SUPPLIERS AND CONTRACT MANUFACTURERS ARE EXPECTED TO TIMELY NOTIFY YOU IN CASE SUPPLY ISSUES ARE EXPECTED?

DOES YOUR CONTRACTS WITH SUPPLIERS ESTABLISH VOLUME PURCHASE GUARANTEES?

DO THESE CONTRACTS HAVE FAILURE-TO-SUPPLY CLAUSES/PENALTIES? IF YES, CAN YOU PROVIDE DETAILS OF THE PENALTIES ENFORCEABLE IN CASE OF SUPPLY DEFAULTS?

PERCENT ORDERS TO BE DELIVERED ON-TIME AND FULL QUANTITY

PERCENT OF REJECTIONS

Some Strategic Questions to answer

IN TERMS OF OVERALL CAPACITY STRATEGY, DOES YOUR COMPANY ADOPT FLEXIBLE MANUFACTURING AND WHAT LEVERS ARE USED TO MEET SUDDEN OR UNEXPECTED INCREASE IN DEMAND?

DOES YOUR COMPANY MAINTAIN REGISTERED SPARE CAPACITY OR STRATEGIC INVENTORY OF KEY INTERMEDIATES AND FINISHED PRODUCTS?

DOES YOUR FACILITY OPERATE ON A SINGLE, DOUBLE OR TREE SHIFTS BASIS FOR THE DRUG PRODUCT THAT WAS SHORT?

IS YOUR MANUFACTURING LINE APPROVED FOR MULTIPLE PRODUCTS OR DEDICATED?

HOW EASE IS THE CHANGE-OVER IN YOUR MANUFACTURING FACILITY? HIGH, MEDIUM OR LOW

DO YOU MEASURE OVERALL EQUIPMENT EFFECTIVENESS (OEE) AND WHAT ARE THE TYPICAL OEE LEVELS?

RANK THE FOLLOWING QUALITY ISSUES IN CAUSING SUPPLY INTERRUPTIONS BASED ON THE OCCURRENCE AND LIKELY IMPACT:

· Rejection due to poor tech transfer process (method)
· Rejection due to operator error (man)
· Rejection due to machine error (machinery)
· Rejection due to outsourced material (material)

Periodic risk assessment reviews

Reports that identify the potential compliance risks across a company's manufacturing supply chain.

Periodic assessment of the supply chain performances

Assess supply chain resilience and shortages in the annual product quality review.

Trending reports

Studies that review past supply chain data trends to forecast potential issues and trigger additional risk assessments.

Issue management communication system

A method that communicates the potential compliance risks across an organization's functional groups and external partners.

Improvement of processes and analytical standards

Improve processes and analytical methods development programs in order to ensure more robust technology transfers to commercial facilities, which improves the opportunity to consistently demonstrate conformance to the established product specifications.

Manufacturer resources for issuing treatment recommendation during shortages of medicinal products

- GMP inspection report identifying or investigating a shortage;
- Outcome of an GMP inspection and regulatory assessment;
- Quality defect reports and assessment;
- Manufacturing problem report and assessment;

– Availability of other strengths or pharmaceutical forms of the same product
– The Marketing Authorization Holder risk assessment of the clinical use of the medicinal product with a defect/GMP noncompliance
– Information on the status of the remaining stock of the affected medicinal product
– Distribution plans of the remaining product in the EU and world wide
– Regular updates on the stock situation of the affected medicinal product (per country)
– Reports on the progress of the corrective actions taken to revert the shortage cause
– Information on the estimated timing of the return to normal production levels
– The MAH's risk assessment of switching patients to other alternatives
– Relevant clinical information: o experience from previous drug shortage(s) (contingency plan on how to deal with a shortage o experience with amended dosing, e.g. lower dose o experience with other medicinal product within the same indication o unpublished clinical data; on-going investigations and clinical trials)

Decision tree on escalation from national to European level

GMP non-compliance/quality defects may lead to a shortage of a medicinal product, if it is decided that it is necessary to prohibit importation and/or release of a batch or to withdraw batches from the market. Though in general such action based on GMP non-compliance/quality defects is good precautionary practice and at the discretion of the Member States when products are authorized nationally, **there might be incidents where it is necessary to elevate the discussion to agree on a harmonized risk management strategy at a Union level in order to protect public health.**

DECISION TREE WOULD FACILITATE THE DECISION ON WHEN SUCH ESCALATION TO A EUROPEAN LEVEL COULD BE CONSIDERED

NO ESCALATION TO EUROPEAN LEVEL IS REQUIRED IF:

a. shortages are limited to a single Member State (although noted that this situation may change over time);
b. the duration of the shortage is limited and not considered relevant from a clinical point of view (e.g. for vaccines, vaccination may be postponed for a few weeks), although this situation may evolve over time

ESCALATION TO A EUROPEAN LEVEL MAY BE CONSIDERED IF:

a. the product is considered to be a critical medicinal product in a Member State and there is evidence that indicates that the shortage will affect more than one Member State. It is possible that there may be differential supply of GMP compliant/GMP non-compliant product between Member States;
b. a decision to keep a suspected defective product on the market may have possible safety implications (e.g. sterility is not guaranteed) that may indicate the need for Union advice on appropriate risk minimization measures to be taken to allow continued use of the suspected defective product;
c. the product at issue is considered to be non-critical but the concern is due to critical GMP non-compliance/quality defects which may affect other products on the Union market;
d. the product is considered to be non-critical but shortages may have an impact on public health (e.g. owing to the number of users or the characteristics of the patient population).

Actions at Union level

Once a Member State or several Member States have decided that an escalation to Union level is necessary, the following principles should be followed in determining which Committee at the Agency should take the lead in the assessment and communication strategy. It is proposed that shortages only affecting centrally authorised products (CAPs) as well as shortages affecting both CAPs and non-CAPs are subject to the CHMP's review. Should more than one Rapporteurship be affected, a lead Rapporteur will be nominated by the Committee. Should a shortage only affect non-CAPs, the Member State(s) should escalate the issue to the Heads of Medicines Agencies CMD(h) for an harmonized response at Union level.

Shortages catalogue

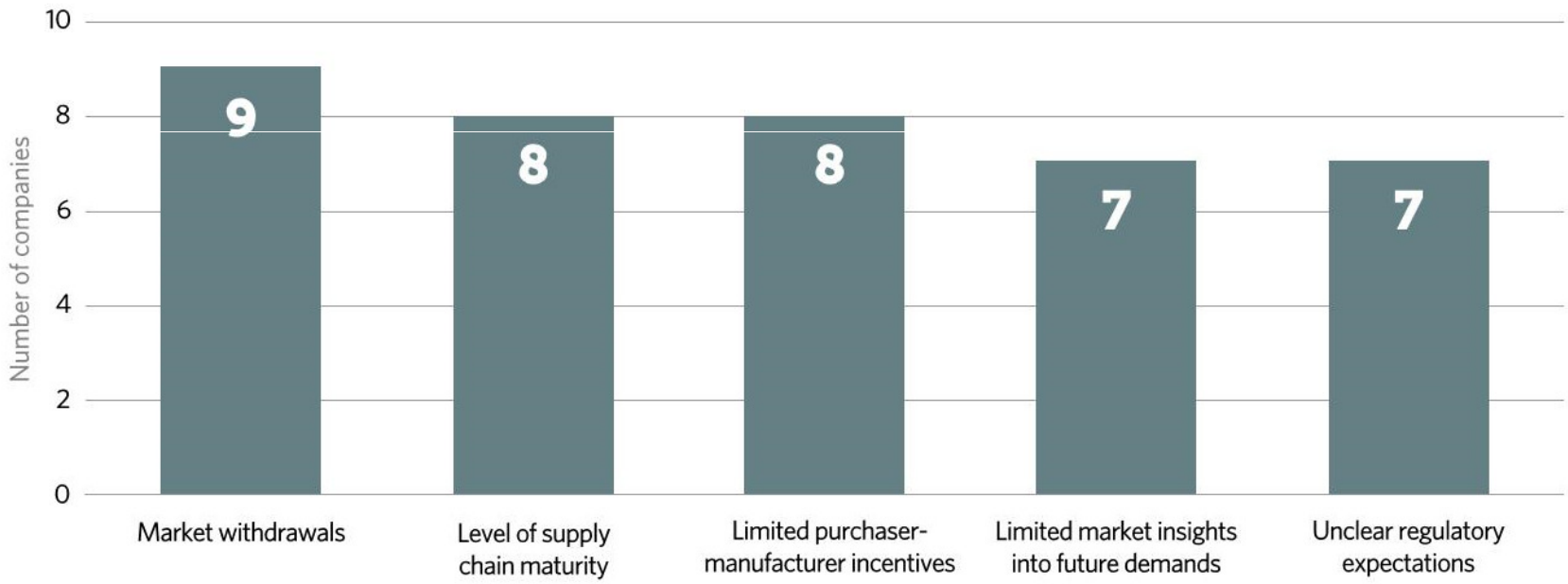
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000376.jsp&mid=WC0b01ac05807477a6

The shortages catalogue contains information on medicine shortages that affect or are likely to affect more than one European Union Member State, where the European Medicines Agency has assessed the shortage and provided recommendations to patients and healthcare professionals across the EU.

Document(s)	Status	First published	Last updated
DepoCyte (cytarabine) supply shortage	Ongoing	19/01/2017	14/03/2017
Cerezyme (imiglucerase) supply shortage	Ongoing	04/11/2013	

It does not give a complete overview of all medicine shortages occurring in the EU, as most shortages are dealt with at a national level.

NO single predictor identified whether a product was at risk of a shortage. There is a set of issues outside of quality that contributed to drug shortages, including the inability to ramp up production when a competitor leaves the market. Among the causes there is also the lack of incentives that would benefit manufacturers when they could produce the product needed to meet demand and prevent a shortage. There are also operational-related elements such as the ability to design predictable, flexible, and redundant supply chains that react quickly to changing demands and/or problems with specific manufacturing sites; predict future demands by improving market insights and navigate regulatory expectations.



Multiple factors outside of quality contributing to drug shortages

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Pharmaceutical Supply Chains I

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Lisbon - April, 26, 2017

European Industrial Pharmacists Group
Groupement des Pharmaciens de l'Industrie en Europe

Questions?

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Thanks for your attention

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