Coping with Drug Shortages through regulatory governance: Approaches and perspectives to a complex global challenge

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AEMPS	Spanish Agency for Medicines and Health Products, Spain
AGES	Austrian Agency for Health and Food Safety, Austria
AIFA	Italian Medicines Agency, Italy
ANM	National Medicines Agency, Romania
ANSM	National Agency for the Safety of Medicine and Health Products, France
ASHP	American Society of Health-System Pharmacists
AT	Austria (ISO 3166 alpha-2)
ATC	Anatomical Therapeutic Chemical Classification System
AU	Australia (ISO 3166 alpha-2)
AUS	Australia
BDA	Bulgarian Drug Agency, Bulgaria
BE	Belgium (ISO 3166 alpha-2)
BfArM	Federal Institute for Drugs and Medical Devices, Germany
CA	Canada (ISO 3166 alpha-2)
CAP	Centralized Authorized Product
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulation
CHMP	Committee Human Medicinal Product
CMD(h)	Coordination Group for Mutual Recognition and Decentralized Procedures - human
CMP	Centralized Medicinal Product
CRC	Consolidated Regulations of Canada
CZ	Czech Republic (ISO 3166 alpha-2)
DCP	Decentralized Procedure
DCP	Decentralized Recognition Procedure
DE	Germany (ISO 3166 alpha-2)
DIN	Drug Identification Number
DKMA	Danish Medicines Agency, Denmark
DS	Drug (Medicine / Pharmaceutical) Shortage(s)
DSS	Drug Shortage Staff
EAHP	European Association of Hospital Pharmacist
EC	European Commission
e-CFR	Electronic Code of Federal Regulation
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EOF	National Organization for Medicines, Greece
EPITT	European Pharmacovigilance Issues Tracking Tool
ES	Spain (ISO 3166 alpha-2)
ETF	EU Executive Task Force
EU	European Union (EEA countries Norway, Island, Liechtenstein are considered as well in this work)
FAMHP	Federal Agency for Medicines and Health Products, Belgium
FDA	Food and Drug Agency
FDASIA	Food and Drug Administration Safety and Innovation Act
FI	Finland (ISO 3166 alpha-2)
FIMEA	Finish medicines Agency, Finland

FR	France (ISO 3166 alpha-2)
GIF	Medical Devices and Biocidal Products Main Pharmaceutical Inspectorate, Poland
GPO	Group Purchasing Organization
GTIN	Global Trade Item Number
HALMED	Agency for medicinal products and medicinal devices, Croatia
HCP	Health Care Professional
HCP	Health Care Professional
hMP	Human medicinal product
HPRA	Health Products Regulatory Authority, Ireland
HR	Croatia (ISO 3166 alpha-2)
HU	Hungary (ISO 3166 alpha-2)
IE	Ireland (ISO 3166 alpha-2)
IGZ	Medicines Evaluation Board; Healthcare Inspectorate, Netherland
IMCA	Icelandic Medicines Agency, Island
IMP	EU Regulatory Network Incident Management Plan
INFARMED	National Authority of Medicines and Health Products, Portugal
INN	International Nonpropriety Name
IRN	Incidence Review Network,
ISPE	International Society for Pharmaceutical Engineering
IT	Italy (ISO 3166 alpha-2)
JAZMP	Agency for Medicinal Products and Medical Devices of the Republic, Slovenia
LV	Latvia (ISO 3166 alpha-2)
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MAPP	Manual of Policies and Procedures
MHRA	Medicines and Healthcare Products Regulatory Agency, United Kingdom
MOH	Ministry of Health Pharmaceutical Service, Cyprus
MP	Medicinal Product
MRP	Mutual Recognition Procedure
MRP	Mutual Recognition Procedure
MS	Member state
MSSC	Multi-Stakeholder Steering Committee on Drug Shortages
n / a	Not available or not applicable
NAP	National Authorized Products
NCA	National Competent Authority
NL	Netherland (ISO 3166 alpha-2)
NOC	Notice of Compliance
Non-CAP	Non-centrally authorized product
NUI	Non-Urgent Information
OGYEI	National Institute of Pharmacy and Nutrition, Hungary
P/T	Provincial / Territorial
PEI	Paul-Ehrlich-Institute, Germany
PRA	Preliminary Risk Assessment
PRAC	Pharmacovigilance Risk Assessment Committee
RA	Rapid Alert
RAVIMIAMET	State Agency of Medicines, Estonia
RMS	Reference Member State
RO	Romania (ISO 3166 alpha-2)
SAM	States Agency of Medicines, Latvia
SOPP	Standard Operating Policy and Procedure (FDA)
SOR	Statutory Orders and Regulations
SUKL	States Institute for Drug Control, Czech Republic
SUKL	State Institute for Drug Control, Slovakia
TGA	Therapeutic Goods Administration

UPC	Universal Product Code
URPL	Office for Registration of Medicinal Products, Poland
US / USA	United States / United States of America
USC	United States Code
VVKT	State Medicines Control Agency, Lithuania
WHO	World Health Organization

ABSTRACT

In developed countries, considerable surplus of pharmaceuticals generally exists. As new products are regularly added in pharmacies, the actual amounts of medicinal products appear high and Drug Shortage (DS) unlikely. However, upon closer inspection of certain classes of medicinal products, such as antibiotics, injectables or cancer products, the portfolio of products is in fact limited and decreases evenly.
In the majority of markets, shortages are rare due to maintenance of equilibrium between the quantity of the products supplied and the quantity of demand. By contrast, the healthcare market is inflexible and constrained in its abilities to react effectively to demand and supply changes. Low price responsiveness influences manufacturer's inventory decisions. This makes the healthcare market particularly susceptible to DS.
DS are a complex and global phenomenon currently on the rise, affecting more than 20 countries world-wide. The causes of DS appear to be multi-factorial with the growing cost pressure in the health sector, and increasing problems with the manufacturing of medicinal products due to high regulatory requirements the major influencing factors. Various stakeholders in the health care system such as patients, pharmacists, and physicians are affected as soon as a medicinal product cannot be delivered to a patient in need. Therefore, strategies to manage and end DS are needed.

This work examined the landscape of DS in the European Union, the United States of America, Canada, and Australia; and provides insights into regulatory strategies used to govern DS situations.

Legal provisions regarding DS were analyzed and it was shown that the legislation in the EU contains provisions for responsibilities of NCAs and MAHs, but no further details regulating DS. In the USA and Canada detailed legal guidance on DS is available, whereas Australia applies a voluntary procedure under control of the TGA.
DS information on the websites of EMA, FDA, Health Canada and TGA appear to be globally aligned, whereas websites of European National Competent Authorities are more diverse. The majority of analyzed reporting websites showed low to medium granularity of information regarding DS, while only a few showed high granularity. The leading regulatory agencies EMA, FDA, Health Canada, and TGA were found to be as heterogeneous as the National Competent Authorities in the EU. Investigations revealed 4 different types of DS reporting systems on the websites: 1) searchable databases, 2) shortage lists 3) tables in PDF or Excel format, and 4) DS information within other reports. It was shown that a well-structured and organized DS reporting system is important for the users to easily and rapidly find that information they need. However, a direct practical benefit of transparent reporting websites was not addressed in this work.

In the EU and USA, the regulatory authorities are responsible for leading DS management strategies, while in Canada and Australia a multi-stakeholder approach is applied. In the USA and Canada new legislations have been introduced that changed the landscape of DS management by handing over more legal power to the regulatory authorities. This is not the case in the EU and Australia. EU-wide, the Incident Management Plan was implemented to cope with DS that affect more than one MS. In the US, FDA was required by law to establish the DS Staff to secure appropriate DS management including rapid notification, reporting, and communication. In Canada, the multi-stakeholder approach to tightly regulate DS management will become mandatory in 2017. In Australia, no provisions are foreseen to force the regulation of the multi-stakeholder approach to manage DS. Although there is no common approach of all countries, it was examined that the three pillars *notification as early as possible*, *structured assessment*, and *coordinated responses* seem to be the most crucial factors. Whether these processes need to be initiated by a higher regulatory body or provisions are required to regulate these processes need to be investigated further.

Regulatory prevention and mitigation strategies were examined and it was found that administrative, legislative, and industry approaches to address DS have focused on the symptoms rather than the causes. Regulatory authorities are constrained in their actions due to limited of legal power. No novel regulatory measurements were implemented except a reporting system. Instead, already existing measures, e.g. expediting reviews, were focused and extended. Potential regulatory actions can be implemented on a short- to long-term perspective and were found to be interdependent to each other. Potential strategies comprise a global pricing system and financial and economic incentives for the pharmaceutical industry, and the development of an essential pharmaceuticals list and a standardized risk assessment including guidance on available treatment alternatives, respectively.

Overall, it could be shown that DS are still an ongoing problem and the termination of DS situations is a challenging and global multi-stakeholder task. Early and rapid notification is the basis to efficiently prevent and mitigate DS and they require distinct and sophisticated management. Various national approaches exist but these need to be aligned more to become globally effective.

AIM OF THIS WORK

DS are a complex and global phenomenon currently on the rise. The causes and relations underlying DS are various and not easy to understand. Every stakeholder in the health care system is affected as soon as a pharmaceutical cannot be delivered to a patient in need; therefore resolution to end DS is urged.
Information on DS situation is crucial for pharmacists and health care professionals for their choice of an appropriate therapy and treatment of patients. Rapid communication and easy access to reliable information on DS is essential.

This work lays out an overview of the landscape of DS in the European Union, the United States of America, Canada, and Australia; and provides insights into regulatory coping strategies. The extent and granularity of available information on DS in these countries is analyzed and the strategy how DS information is relayed to various stakeholders in the health care system is investigated.

Furthermore, applied DS reporting systems are examined, and their impact on various stakeholders in the health care system is compared. The development and implementation of management strategies to resolve DS in these countries are analyzed, and proposals to improve the current set of mitigation and prevention methods by enhancing regulatory governance are made.
This work provides insights on how the complex and global phenomenon of DS can be controlled by enhancing regulatory governance in future.

I. DRUG SHORTAGE AS GLOBAL CHALLENGE

I.A. The challenge of finding a definition

DS are a complex and global phenomenon currently on the rise, affecting more than 20 countries world-wide.[73] The causes appear to be multi-factorial (Chapter I.A). Various stakeholders in the health care system are affected as soon as a pharmaceutical cannot be delivered to a patient in need.

To allow an appropriate analysis and interpretation of the word-wide shortage situation, the underlying definition is important. Depending on the country, the definition and scope of *pharmaceuticals* referred to in the respective legislation might be different. In the EU, the term *medicinal product* and in Australia the term *medicine* is used. In the USA and Canada the term *drug* is used instead. Besides, several definitions for medical devices and classification systems e.g. to distinguish food supplements from medicines and devices are available.
In this work, a general approach was taken and shortages of pharmaceuticals are abbreviated as *drug shortages (DS)*; however, this term refers to the legal term in the respective legislation of the country.

An overview of DS definitions used in the EU, the US, Canada, and Australia is given in Table 1.

Table 1 Overview of DS definitions

Country	Institution	Definition
EU	EMA (2014)*	When the delivery of a medicine cannot comply to the needs of the patients, whether this is local, national, or international.
	EMA[30]	Medicines Shortages that affect or are likely to affect more than one EU MS, where the EMA has assessed the shortage and provided recommendations to patients and healthcare professionals across the EU.
	ISPE[70]	A situation in which the total supply of an approved (by the appropriate Health Authority) drug is inadequate to meet the current or projected demand at the user level.
	EFPIA[71]	A potential Drug Shortage is defined as: the occurrence of internal or external situations (single or in a combination of both), which result in an interruption of supplies of a medicinal product, if not properly addressed and controlled.
USA	FDA[38]	A period of time when the demand or projected demand for the drug within the United States exceed the supply of the drug. In general, the DSS focuses on shortages of medically necessary product that have a

* definition was formulated in 2014, but was removed from the EMA website[66]

		significant effect on public health.
	ASHP[72]	A supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent.
Canada	Health Canada[35]	A Drug Shortage is a situation when a manufacturer or importer of a drug cannot meet actual or projected demand. Drug Shortage can include temporary disruptions or permanent discontinuances in the production and supply of a drug.
	Canadian Drug Shortage database[68]	As soon as a market authorization holder knows that it will take longer than 20 days to supply a drug to meet expected patient volumes on an ongoing basis, they will report this as a shortage on the communications platform. It is understood that the inability of a patient to receive their prescribed medicines at the first attempt to fill a prescription may not constitute a drug being in 'shortage,' as the drug may be available in other pharmacies or within the wholesale or distribution network (i.e., pharmacy supply chain), usually within a few days.
Australia	TGA[69]	A Medicine Shortage occurs when the supply of a medicine is not likely to meet the normal or projected consumer demand for the medicine within Australia for a period of time. Most of this shortage information is provided to us voluntarily by the sponsor of the prescription medicine.

In 2014, EMA formulated a definition of DS, which is no longer on the website[66]. The Shortage Survey by EMA in 2015 revealed that the national legislation of 18 out of 28 participating MS do not include a definition for DS. The national legislation of 21 out of 28 MS requires mandatory notification of DS[45].
In summary, the survey found that there is no common definition of DS in the EU. However, MS holding a definition in the national legislation addressed similar categories in their definition, such as the adequate supply, the length of the DS, and the severity/clinical impact of the DS.

In the analysis, some countries had more than one definition for DS (Table 1).
This might be explained by the diversity of stakeholders concerned with DS. Due to different roles and responsibilities, definitions in the national legislation have other purposes than the definitions of professional organizations[66]. Again, no common definition is available although similar categories in their definition can be identified.

The problem of not having a common definition for DS was also acknowledged by the WHO earlier[73]. Recently, WHO highlighted, that existing databases have different definitions and approaches, and that it is essential to harmonize *stock-out* and *shortage* definitions because not every stock-out leads to a DS[65].

In general, it is suggested that a distinction between a *definition of DS* and a *definition used for reporting DS* should be made[66,65]. However, regarding the reporting definition, there needs to be evaluated further whether this considers the reporting of a DS by the MAH, wholesaler, or any stakeholder to the regulatory authority or reporting of the regulatory authority after an appropriate assessment, e.g. in terms of publishing the DS case on a website.

For the sake of clarity, *notification* is used in this work to indicate the initial notification of a DS situation to the regulatory authority and *reporting* means the communication from the regulatory authority on to other stakeholders, such as physicians, pharmacists, or patients.

A common definition of DS facilitates the communication between different stakeholders including patients and also international benchmarking. Furthermore, it would allow comparing national databases and the results of scientific studies to understand the scale of the problem. With a common definition, DS could be objectively assessed, which helps to understand whether a DS is a national or international concern. Hence, this information can help to find a rapid solution and take appropriate action against DS by industry as well as agencies.

Five essential elements were found to be important for a definition: 1) the level of DS (patient, pharmacy, wholesaler level), 2) supply problems (demand and supply side, delivery and availability of pharmaceutical), 3) permanent or temporally DS, 4) typology of the pharmaceutical, and 5) time frame[45,66,67].
In some countries, prices of pharmaceuticals are subject to free-market principles, which can lead to DS. Hence, it should be reconsidered, if DS from an economic point of view should be defined as well[66]. Primarily, this might apply to high-income countries only, as low- and middle-income countries may not have been considered in the various studies[65]. However, it should be discussed if only one or a global definition of DS applies.

I.B. Prevalence, duration, and pharmaceuticals affected

Studies on DS up until 2011 were published mainly in US literature; however recently, DS research emerging from the EU, Canada, and Australia is more widely accessible. In all countries, studies investigating DS scope, causes and impact are available, although the results of these studies are challenging to compare due to the differences in the underlying definition of a DS (Chapter I.A)[66].

DS have been increasing in recent years, although the worldwide prevalence of DS world-wide is unknown[74]. WHO reported in 2012 more than 20 countries were affected by DS[73] including high-, middle-, and low-income countries[65]. In 2014, the EAHP conducted a questionnaire-based survey amongst EAHP members[77]. Participation in the survey included 537 hospital pharmacists from 36 countries. Of European Hospital pharmacist, 45.2% experience DS on a weekly basis, 21.2% on a daily basis[77]. In terms of delivering the best care to patients and operating the hospital pharmacy, 86.2% stated that DS are a current problem in their countries. Another report based on literature search found that DS situations occur in several EU MS[75] with almost all EU MS coping with DS situations[75]. In this work, 58% of all agency website make DS a clear subject of discussion (Chapter II).

In the US and Canada, DS situation are constantly reported by the FDA[33] and AHSP[72], and the Canadian Drug Shortage Database, respectively[68]. Likewise, in Australia DS has been an issue for several years and is still being reported[76,82].
This shows that DS are known since decades and still an issue in the EU affecting various stakeholders in the health care system, such as pharmacist, physicians, patients, and regulatory authorities.

In terms of duration, 63.3% of European Hospital pharmacist experienced DS lasting for several weeks, 29.7% for a number of months, and some also experienced DS lasting several years[77]. One study examined a median duration of a DS in the EU of 139 days[75]. Yet, this is not illustrative for all occurring DS due to the specificities of each pharmaceutical. For instance, in the US, listed DS starting in 2014 or earlier are still not yet resolved[33]. This is similar for cases reported in the shortage databases in Canada[68] and Australia[57].

Due to the high diversity and specific properties of pharmaceuticals, some classes are more susceptible to DS leading to recurrent DS (Chapter I.A). Although it is challenging to compare entries in DS databases due to different definitions, using the ATC system may help standardize the comparison of pharmaceuticals affected by DS.
DS of pharmaceuticals for preserving and sustaining life mostly occur in the EU[78,79], US[80], Canada[81], and Australia[76,82]. Of these, include orphan and pediatric pharmaceuticals; chronic diseases, emergency and cancer medicines, antibiotics and anesthetics[65]. WHO defines approximately 30% of essential medicine pharmaceuticals with a shortage affect in the EU[78]. All major therapy areas have products on the DS lists[80]. Furthermore, studies show that generic pharmaceuticals (EU[79,] 56%; US[80], 83%) rather than branded pharmaceuticals (EU[79], 35%; US[80], 11%) cause DS. Although, in some EU countries, higher numbers of originator (patented) products is reported in short supply (51.8%)[77].
Regarding the dosage form, most DS are found to belong to injectables and oral pharmaceuticals[78,80].

I.C. Causes and impacts of DS situations

To support the development of appropriate prevention and mitigation strategies of DS, it is important to understand the causes of DS and to analyze the consequences.
As an analysis of the causes and consequences of DS is not within the scope of this work a brief overview is given.

The pharmaceutical market from raw material to patient and pricing is a highly complex topic[78,83,84]. Causes of DS appear to be multi-factorial and multi-layered; therefore it seemed reasonable to summarize the causes for DS in *predictable causes* and *unpredictable causes* (Table 2)[84].

Table 2 Predictable and unpredictable reasons for DS

This overview is taken from reference[84].

#	Unpredictable	#	Predictable
1	Natural Disasters	**1**	Product discontinuation
2	Manufacturing problems	**2**	Industry consolidation (M&A)
3	Raw Material Shortages	**3**	Limited manufacturing capacity
4	Non-compliance with regulatory standards	**4**	Just-in-time inventories
5	Packaging shortages	**5**	Rationing / quotas
6	Unexpected demand	**6**	Deliberate shortages to manipulate price
7	Epidemics	**7**	Market shifts
8	Parallel distribution	**8**	Launch of a new competitor/formulation, or patent expiry
9	Competitive issues		
10	Foreign exchange effect		
11	Sovereign issues (financial crisis, debt, default)		

The mentioned causes for DS can be divided into key areas that cover much of the above: 1) Economic, 2) Business, and 3) Supply Chain[84]. The particular cause of a DS may be in relation to several other causes of the three areas (Figure 1). This is why a case-by-case basis of the underlying cause of a current DS is needed; however it may not apply to other DS.

Most causes of DS in the EU[67,83], the US[85], Canada, and Australia[76,82] can be related to manufacturing including technical issues, contaminations and impurities, monopoly on raw materials, increased and shifts in demand, and changes in compliance with regulatory requirements. Also supply problems including levels of stock, quotas and rationing, and transportation issues are a predominant cause for DS[67,84,85].

Globally, the price component was revealed to be an important determinant of DS[67,84].
Pricing procedures for patented and generic pharmaceuticals; and purchasing strategies, including reference pricing and tendering have significantly impacted DS[67]. For instance, financial pressure and economic crisis, smaller markets, such as Canada or in the case of Belgium in the EU, or low priced countries, might not be given the highest priority of the pharmaceutical industry, thus essential pharmaceuticals might not be available[75,86] .
In contrast to the US, Canada, and Australia, where parallel distribution is not permitted and shortages are thus clearly linked to other factors; parallel distribution in the EU is encouraged by authorities in a number of markets in order to reduce their spending on pharmaceuticals[86].
The business case for exports of pharmaceuticals from low priced countries (e.g. Poland, Greece and Spain) is compelling for parallel distributors[83]. However, if the exporting country exceeds the national stocks and cannot comply with the national demand for a particular pharmaceutical, which is often the case, parallel export results in DS[83]. To this end, quota systems have been implemented to ensure products destined for one market remain in the market to meet local demand and to reduce parallel distribution. This approach did not prevent DS from occurring; it effectively has become a filter and effectively has created a class of shortages in its own right[83].
With Poland having among the lowest prices in Europe, the level of parallel exports did not increase over the past few years but remained largely stable, similar to Spain, where parallel distribution has declined in recent years[83]. Greece represents a prime location for wholesalers to buy cheap pharmaceuticals for re-export due to the cuts in prices for innovative and generic products; however, the overall turnover of parallel exports is constant and decreasing if referring to official figures of EOF. Moreover, in the UK, shortages in generics are on the rise as well although generics are generally not subject to parallel distribution[83]. These examples show that parallel distribution might not be an explicit cause but a symptom that facilitates DS situation, particularly in low priced European countries.

The causes of DS are divers and the impact widespread.
Patients in need are affected the most by DS[73]; in adequate delayed or denied treatment, as well as medication errors and higher safety risk due to alternative, unfamiliar pharmaceuticals or treatments have been documented[85,87]. In some cases, even death was reported[85].
Hording and stockpiling of pharmaceuticals by patients, HCP, and pharmacies has been experienced[83]. Higher hospital expenses and increased labor costs are consequences of DS[77,85]. Also, DS may pose an entry for increased falsified medicines on the gray market since patients and HCP are not familiar with substation pharmaceuticals[88,90].

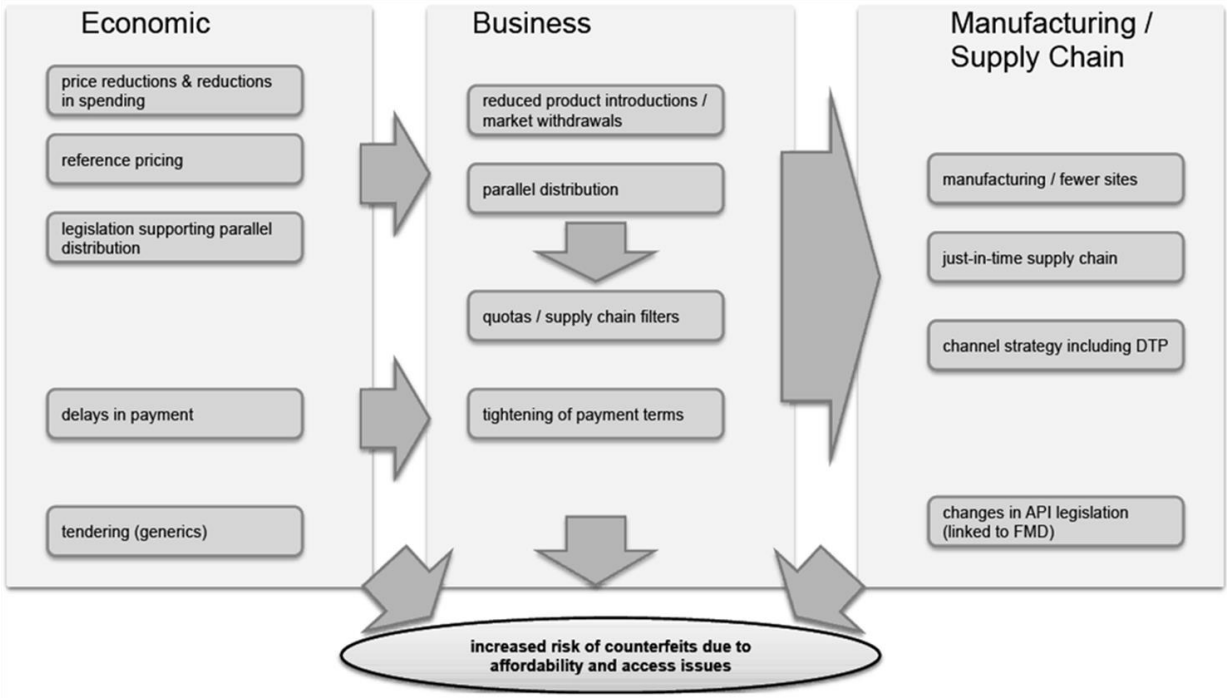

Figure 1 Overview and relationship of the causes of DS

This overview is taken from reference[84].

I.D. Legal requirements and responsibilities

The entire pharmaceutical market is highly regulated by legislations and guidelines within each country. Therefore, a closer look into these legislations is necessary to gain insights about the legal landscape describing responsibilities, requirements, and obligations of MAHs, manufacturers, and agencies; and how countries deal with problems of DS.

The current[†] effective legislation of different countries regarding requirements and responsibilities of MAHs, manufacturers, and agencies are shown in Table 3.

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[†] At time of compiling this work (August – November 2016)

Table 3 Overview of legal requirements and responsibilities in regard to DS

Country	Legislation	Key information
European Union	Regulation (EC) No 726/2004 Number (28) Article 13 (4) Directive 2001/83/EC Article 23a Article 81 Article 123 (1) Dir 2003/94/EC Article 13 (1)	 Responsibilities of the Agency Requirements for MAHs for market supply of central MP Requirements for MAHs for market supply of MRP, DCP MP Requirements for MAHs and wholesalers for market supply Responsibilities of NCA Requirements of manufacturers
United States of America	CFR, title 21 §310.306 b §310.306 c §314.81 §600.82 USC, title 21 Sec. 356c Sec. 356c-1; Sec. 356d and e Sec. 356f	 Requirements of manufacturers Responsibilities of the FDA Requirements of applicants Requirements of applicants / responsibilities FDA regarding biologics Requirements of manufacturers Responsibilities of the FDA Legal exclusion for health system entities
Canada	CRC, Food and Drug Regulation C.01.014.3 C.01.014.7 Canada Gazette, *SOR/2016-139*[B]	 Requirement of manufacturer or importer Requirement of a person who has been assigned a drug identification number[A] Requirements and responsibilities of MAHs and Health Canada
Australia	Therapeutic Goods Act 1989 Therapeutic Goods Information (Medicine Shortages Information Initiative) Specification 2014	 Specifications define the kinds of therapeutic goods information that the Secretary may release to the public via respective website

[A] terminology used in CRC; refers to MAH as termed in EU legislation
[B] not yet effective

I.D.1. European Union

Requirements for market supply of human medicinal products

Under Regulation (EC) No 726/2004 it is currently stated that MAH of a centralized human MP shall inform the Agency after granting the authorization *"[…] of the dates of actual marketing […] in the Member States*"[1]. In addition, MAHs in the EU are required to notify the Agency if the MP "*ceases to be placed on the market, either temporally or permanently […] no less than two months before interruption […] and shall inform the Competent Authority of the reasons for such action […].*"[1] For MP authorized under the scope of Directive 2001/83/EC, the same legal procedure applies, however NCA of the respective member states are addressed instead[2].

With regard to the market supply of medicinal products, the MAH and authorized wholesalers must *"[…] ensure appropriate and continued supplies […] so that the needs of patients in the Member State in question are covered."*[5]
In addition, manufacturers of a MP are obliged to inform the NCA in case of a recall or abnormal restriction on supply in the distribution network. However this exclusively applies to quality defects of the MP[6], and excludes other reasons such as problems within the supply chain or economic business related reasons.

Responsibility of the Agency and NCAs
Regulation (EC) No 726/2004 states that *"[…] in order to create greater legal certainty it is necessary to confer on the Agency powers to monitor the distribution of medicinal products authorised by the Community and to specify the sanctions and the procedures for implementing them in the event of failure […]."*[3] In comparison, for MP authorized under the scope of Directive 2001/83/EC "*each Member State shall take all the appropriate measures to ensure that decisions authorizing marketing, refusing or revoking a marketing authorization, cancelling a decision refusing or revoking a marketing authorization, prohibiting supply, or withdrawing a product from the market […]."*[4] However, no further details on how to implement can be found in the Regulation or Directive.

In summary, the legislation in the EU defines responsibilities of NCAs and MAHs, and also touches the topic of temporally or permanently interrupting market supply of MP. For DS caused by reasons other than quality defects, no laws are available on the EU level.

I.D.2. United States of America

In contrast to the EU, jurisdiction in the USA is more advanced and specific in terms of regulating DS.

Requirements for market supply of human medicinal products
Unlike the EU, MAHs are not legally obligated to notify the FDA of the actual marketing dates of the MP after granted authorization. However, the FDA needs to be notified of permanent discontinuance or interruption in manufacturing of MP by manufacturers[7] and applicants[‡,11]. This provision exclusively applies for prescription pharmaceutical products that *"[…] lead to a meaningful disruption in supply of that drug in the United States […]"*[9,11]. This restriction to a particular class of MP is not statutory in the EU. Interestingly, corresponding provisions for biological MP are codified separately in the legislation[10].

Responsibility of the FDA
Responsibilities of the FDA regarding DS are specifically defined in the legislation. The FDA is obliged to "*[…] maintain a publicly available list of drugs […] in shortage"* that satisfies legally binding criteria[8,14]. Furthermore, the FDA shall submit to the Congress an annual report on DS for updates on defined subjects described in the legislation[12].

[‡]terminology used in CFR and UCS; refers to MAH as termed in EU legislation

To prevent and mitigate DS, the FDA is establishing a task force to develop and implement a strategic plan for enhancing FDA's response[13]. Besides this, the legislation also includes a proactive provision permitting hospitals in times of DS to repackage and transfer a pharmaceutical to another hospital within the same health care system[15].

I.D.3. Canada

Until now, the Canadian *Food and Drug Regulations* have no provisions specific to DS[16]. However, a provision mandating the notification of the date on which a pharmaceutical was first sold in Canada[17], and the notification of discontinuation of the sale of a market-approved pharmaceutical to Health Canada within 30-days[18] is available.
On June 14, 2016, regulations amending the Food and Drug Regulations with regard to shortages of pharmaceuticals and discontinuation of sale of pharmaceuticals were published[19]. These will come into effect no earlier than March 2017[19]. Therein, 1) the information to be provided by the MAH regarding the notification of discontinuance is further specified[20], and also the corresponding legally binding time plan[22], 2) MAHs are mandated to report upcoming shortages and discontinuances of a defined scope of MP[22] to a website that is operated by a third-party controlled by Health Canada[23] , and 3) MAHs are required to notify Health Canada if a pharmaceutical has not been sold on the Canadian Market for a period of 12 consecutive months[24].
Essentially, "*the Canadian amendments will outline the specific types of products that will be subject to the Regulations"* and "[…] *the amendments will bring Canada into alignment with the U.S. FDA and the European Medicines Agency […]*"[25].

I.D.4. Australia

Similar to Canada, but in contrast to the EU and the USA, the Therapeutic Goods Act 1989[26] in Australia, and the Therapeutic Goods Regulations 1990[27] do not contain provisions specific to DS. However, in 2014 Australian authorities revised the Therapeutic Goods Information (Medicine Shortages Information Initiative) Specification 2014[28].
The purpose of the Specification is to provide a legal basis under the Therapeutic Goods Act 1989 to support the release of therapeutic goods information to the public[29]. This information is published on a searchable webpage on the TGA's website[29]. The kind of information that the Secretary is able to release is listed in Schedule 1 to the Specification[28].
Information specific to DS will be primarily provided by the sponsor[§] of the pharmaceutical on a voluntarily basis; notification is not legally binding. However, TGA may receive and evaluate information regarding DS, and publish it on the website, independent of sponsor participation. Herewith, "*early communication of information about current or anticipated shortages of prescription medicine assists health professionals to make informed decisions about the continuity of care of their patients*" [29].

[§] terminology used in the Therapeutic Goods Information; refers to MAH as termed in EU legislation

I.D.5. Summary:

Provisions regarding DS in the legislation of the 4 industry nations, the EU, USA, Canada, and Australia have been examined.

The legislation in the EU contains provision about responsibilities of NCAs and MAHs, but does not contain further details regulating DS.
On the contrary, provisions are adopted in the USA and Canada that give detailed legal guidance on DS; however, this guidance is slightly different in both nations.
No provisions on DS are incorporated into the legislation in Australia, but a voluntary notification and reporting procedure under control of the TGA is available.

II. AVAILABILITY OF INFORMATION ON DS

Information on DS situation is crucial for pharmacists and HCP for the choice of an appropriate therapy and treatment of patients. Therefore, rapid communication and easy access to reliable and plausible information on DS is essential.

In the first part of this Chapter (II.A) the extent of agency website transparency for publicly accessible information on DS in the European Union, Australia is discussed. The second part of this Chapter (II.B) investigates DS reporting systems in the European Union, United States of America, Canada, and Australia in more detail. The organization and content of DS information presented on the respective websites is examined.

II.A. Transparency of information

Regulatory bodies are responsible for pharmaceuticals in order to achieve high quality, safe and beneficial pharmaceuticals for patients. Websites of regulatory authorities are often used by a wide range of people like patients, pharmacists, HCP, and industry. Therefore, it is an optimal platform to collect and distribute important information about pharmaceuticals and DS situations in the country.

To get insights if and what DS data is published, public domains from regulatory authorities have been accessed and scanned for respective information. If no information could be found after first scanning, a manually search was performed using the vocabulary 1) *Drug / Medicine Shortage(s)*, 2) *out-of-stock situation(s)*, 3) *reporting*, and 4) *database*. In a few cases, vocabulary 1) - 4) had been translated into further European Languages, as indicated accordingly**.

Described below are the survey results for the European Union, United States of America, Canada, and Australia.

II.A.1. European Union

EMA offers a hyperlink to important key webpages regarding DS on the homepage for fast navigation. Two subpages on the EMA website are devoted to DS with reference to overall guidance documents such as reflection papers, and a shortage catalogue[31]. Information published on the website does not cover the entire DS situation in Europe. For further information, references are given to websites of NCAs in the EU[32].

** When information was not available in English, the national language was used for evaluation. Web-based translators were utilized supportively (http://dict.leo.org/ende/index_de.html; https://translate.google.de/).

The EMA website as well as by EMA referenced websites of NCAs[32] have been accessed and screened for available information. An overview of the results accumulated during the survey is summarized in Table 4 and statistics thereof are presented in Figure 2.

Table 4 Information on DS at websites of NCAs in EU and EEA as references by EMA

Country	Institution[A]	Information available?	Notes
EU	EMA European Medicines Agency	Yes, public	Hyperlink "*Medicines Shortages*" on homepage for fast navigation available
Austria	Austrian Agency for Health and Food Safety (AGES); Bundesamt für Sicherheit im Gesundheitswesen (BSAG)	Yes, public - only in German	No information on AGES website as indicated by EMA, but on website of associated authority (BSAG)
Belgium	Federal Agency for Medicines and Health Products (FAMHP)	Yes, public - only in Dutch	n / a
Bulgaria	Bulgarian Drug Agency (BDA)	No, none	n / a
Croatia	Agency for medicinal products and medicinal devices of Croatia (HALMED)	Yes, public	n / a
Cyprus	Ministry of Health Pharmaceutical Service (MOH)	No, none	n / a
Czech Republic	States Institute for Drug Control (SUKL)	Yes, public	n / a
Denmark	Danish Medicines Agency (DKMA)	No, none	No search engine on website
Estonia	State Agency of Medicines (RAVIMIAMET)	No, none	n / a
Finland	Finish medicines Agency (FIMEA)	Yes, public - only in Finish	n / a
France	National Agency for the Safety of Medicine and Health Products (ANSM)	Yes, public - only in French	n / a
Germany	Federal Institute for Drugs and Medical Devices (BfArM); Paul-Ehrlich-Institute (PEI)	Yes, public - only in German	Search in English does not lead to information on DS except information letters (BfArM)
Greece	National Organization for Medicines (EOF)	Yes, but restricted	Log-in data required
Hungary	National Institute of Pharmacy and Nutrition (OGYEI)	Yes, public - in Hungarian	Hyperlink "*Temporary Drug Shortages*" on homepage for fast navigation available
Iceland	Icelandic Medicines Agency (IMCA)	No, none	n / a
Ireland	Health Products Regulatory Authority (HPRA)	Yes, public	Information within safety notices
Italia	Italian Medicines Agency (AIFA)	Yes, public - in Italian	n / a

Latvia	States Agency of Medicines (SAM)	Yes, public	n / a
Liechtenstein	Office of Health, Dep. of Pharmaceuticals	No, none	n / a
Lithuania	State Medicines Control Agency (VVKT)	No, none	n / a
Luxembourg	Ministry of Health	No, none	n / a
Malta	Medicines Authority	No, none	n / a
Netherlands	Medicines Evaluation Board (IGZ); Healthcare Inspectorate	Yes, public	n / a
Norway	Norwegian Medicines Agency	No, none	n / a
Poland	Office for Registration of Medicinal Products (URPL); Medical Devices and Biocidal Products Main Pharmaceutical Inspectorate(GIF)	No, none	Privately funded website available, not referenced
Portugal	National Authority of Medicines and Health Products (INFARMED)	Yes, but restricted	Log-in data required
Romania	National Medicines Agency(ANM)	Yes, public	Information within important notifications
Slovakia	State Institute for Drug Control (SUKL)	No, none	Medicinal Product Database, but no information on DS
Slovenia	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP)	No, none	List of indispensable pharmaceuticals, but no information on DS available
Spain	Spanish Agency for Medicines and Health Products (AEMPS)	Yes, public - in Spanish	n / a
Sweden	Medical Products Agency	Yes, but restricted	Log-in data required
United Kingdom	Medicines and Healthcare Products Regulatory Agency (MHRA)	No, none	Pharmaceutical Services Negotiating Committee publishes information, not referenced

[A] see Annex I for address of website

Figure 2 below presents the statistics of the analysis of the information from the survey on information regarding DS on authority websites.

Less than half of the screened websites (45%) contain information on DS that are publicly available, either in English (19%) or in the national language (26%). Publication of information in the national language of the respective member state however, appears acceptable as the website is intended for a defined nationality in the EU.
Only the Hungarian authority website allows easy navigation via a hyperlink on the start homepage including the use of search engines lead to information on DS. For some authority websites (e.g. Ireland and Romania) information are challenging to find and more than half of the websites (55%) do not contain publicly available information on DS. Moreover, 10% of

NCA websites including the three countries Greece, Portugal, and Sweden, do allow access to further information or databases only after registration and log-in to the respective website.

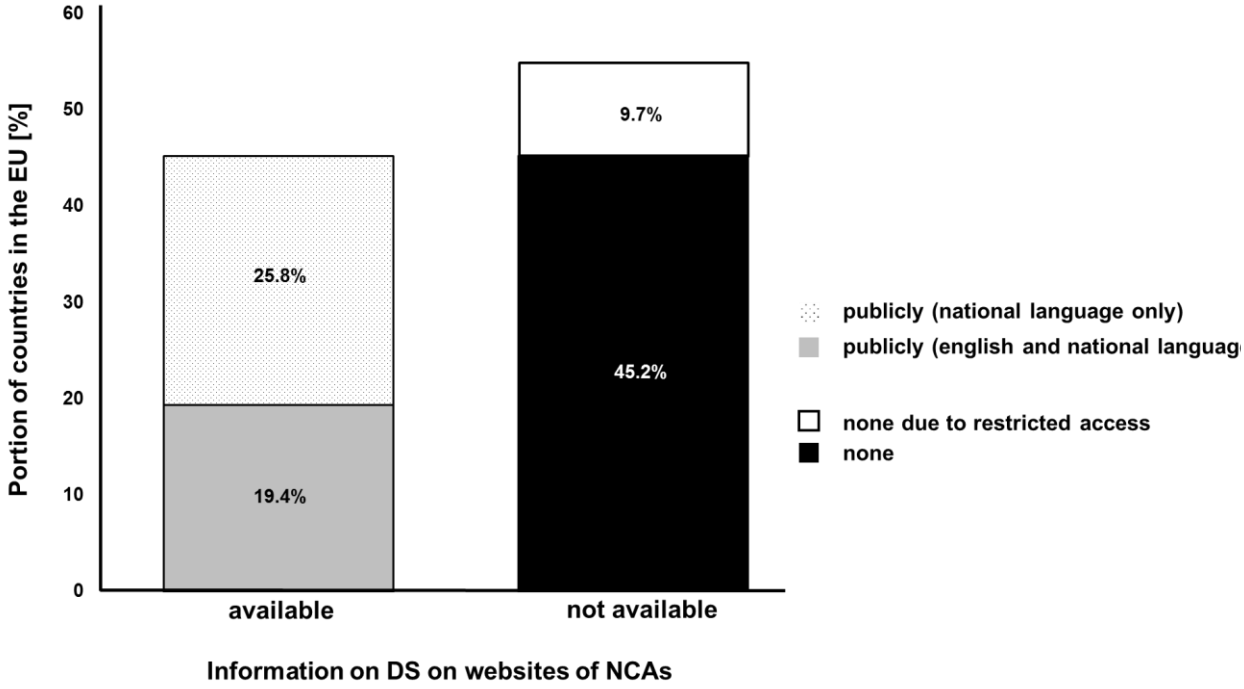


Figure 2 Information on DS on websites of NCAs

Websites of NCAs have been accessed and scanned for information on DS. If no information could be found after first scanning, a manually search using the search engine was performed. The following vocabulary was used: 1) Drug / Medicine Shortage(s), 2) out-of-stock situation(s), 3) reporting, and 4) database. In a few cases, vocabulary was translated into the national language of the member state. Addresses of respective websites are listed in Annex I.

Essentially, the level of information on DS on the websites of NCA in EU and EEA is quite varied. While some websites allow easy access to information on DS, others are more challenging to access, or do not offer any information at all.

II.A.2. United States of America, Canada, and Australia

As already learned from the previous Chapter, guidance on DS is more advanced and specific in the USA, Canada, and Australia as compared to the EU (Chapter I.D.1). Interestingly, this is not reflected in terms of publicly available information on agency websites.

Information on DS that is publicly available on the EMA website[31] was easily accessible (compare with Chapter II.A.1). This was similar for information on websites of the FDA in the USA[33], the TGA in Australia[34], and Health Canada in Canada[35] (summarized in

Table 5). Importantly, the Health Canada website general guiding information is available, while reference to a third-party website is given for current shortage information.

Table 5 Information on DS at agencies' websites of selected countries

Country	Institution[A]	Information on DS available?	Notes
EU	European Medicines Agency (EMA)	Yes, public	See Table 4
USA	Food and Drug Administration (FDA)	Yes, public	n / a
Canada	Health Canada	Yes, public	Drug Shortage Records are not maintained by Health Canada
Australia	Therapeutic Goods Agency (TGA)	Yes, public	n / a

[A] see Annex I for address of website

II.A.3. Summary

The availability of information on DS published on websites of agencies in the EU, the USA, Canada, and Australia was examined.

In summary, the availability of information on DS published on websites of NCA in EU is quite varied. A uniform template regarding e.g. the organization of websites to present information on DS is not available. In contrast, EMA, FDA, Health Canada, and TGA websites appear to be globally aligned and the organization of each website allows quick access to publicly available DS information. However, the practical benefit of a transparent reporting websites is not evident and still needs to be demonstrated.

II.B. Public DS reporting systems

Public DS reporting systems offer information particularly to pharmacists and HCP supporting therapy and treatment decisions. An ideal reporting system would allow filed data to be easily and rapidly available once the user requests information. Ideally, this data should reflect the real-time situation.

After a general survey about DS information on websites of regulatory bodies, the public DS reporting systems are examined here in more detail. In particular, the type of reporting system, the scope of pharmaceuticals and the level of details that are reported are examined.

II.B.1. European Union

EMA is the central competent agency in the EU and publishes the shortage catalogue on the EMA website[31]. The shortages catalogue contains information on DS that affect or are likely to affect more than one MS but does not give a complete overview of all DS occurring in the EU, as most shortages are dealt with at a national level[31].

DS reporting systems on the EMA website and NCA websites respectively have been accessed and scanned for information regarding the type of reporting system and the scope of products. An evaluation matrix (compare Annex II) was established to evaluate the presented level of detail about information on DS. This normalizes the available information for a better comparison. For each defined category a score of one point was given. In total 32 categories were examined with 32 points being the highest possible score to reach.

In general, 4 different DS reporting system were found on the websites: 1) a searchable database, 2) a table as PDF or Excel sheet for download, 3) listings on a webpage, and 4) information only within other information such as letters from manufacturers.

With regards to the reporting system on NCA websites, the scope of products published mainly focusses on human MP. The calculated numbers representing the level of detail are between 7 (Ireland) and 20 (Czech Republic) out of 32. This indicates huge differences in the DS reporting systems of NCA. Table 6 presents an overview to the examination.

Table 6 DS reporting systems in the EU

DS reporting systems published on the websites of NCAs have been scanned for respective information. Only these websites were accessed that were identified before publishing information on DS (Chapter II.A.1).

Country	Institution	Type of reporting system	Scope of products	Level of detail[A]	Notes
EU	EMA	Shortage catalogue in table format; detailed information in PDF format available	1) Human MP 2) CAPs / Non-CAPs 3) ≥ one MS is affected,	11	Reference to websites of NCAs for; no complete

			or likely to be affected 4) Status "DS of critical MP" as per Definition that require actions on Union level[36, 37]		overview of DS in the EU possible
Austria	BSAG	Shortage list as table in PDF format	Human MP	11	n / a
Belgium	FAMHP	Shortage list as table in PDF format	Human/ veterinary MP	11	n / a
Croatia	HALMED	Shortage list as table in PDF format	Human MP	11	Discontinuations separately
Czech Republic	SUKL	Database comprehensive info more than DS	Human MP	20	n / a
Finland	FIMEA	Shortage overview on website; detailed information in PDF format	Human/ veterinary MP	15	n / a
France	ANSM	Shortage overview on website; details for each MP, information letter from MAH published	Human MP	16	n / a
Germany	BfArM; PEI	Shortage list as table in PDF format, reference to homepage for further details regarding substitutes	Human MP	14	One list compiled by both institutes
Hungary	OGYEI	Shortage list as Excel sheet for download	Human MP	11	Discontinuations separately
Ireland	HPRA	Within "safety information", only HCP letters from MAHs available, content not standardized	Human MP	7	Challenging to find, only via web search with "Shortage"
Italia	AIFA	Shortage list as table in PDF format	Human MP	15	n / a
Latvia	SAM	Shortage list on website	Human MP	11	n / a
Netherlands	IGZ	Searchable Database comprehensive info for each MP	Human MP	14	Orphan MP are highlighted
Romania	ANM	Within *important notifications*	Human MP	8	Challenging to find
Spain	AEMPS	Searchable database; comprehensive information for each MP	Human MP	13	n / a

[A] see Annex II for evaluation matrix, and Figure 3 for a summary

II.B.2. United States of America, Canada, and Australia

Similar to the EU, regulatory bodies in the US, Canada, and Australia publish DS reporting systems on their websites. The same types of DS reporting systems used in the EU are also available in the US (searchable database), Canada (listings on a webpage), and Australia (searchable database).

The scope of pharmaceuticals published seems to be similar, although only human MP is considered. The calculated score of the level of detail is ranging from 15 (USA and Canada) to 20 (Australia). This indicates that the DS reporting systems contain more information about the shortage situation than these in the EU. An overview of the examination is shown in Table 7.

Table 7 DS reporting systems in the USA, Canada, and Australia

DS Reporting systems published on the websites of NCAs have been scanned for respective information. Only these websites were accessed that were identified to publish information on DS (Chapter II.A.2).

Country	Institution	Type of reporting system	Scope of products	Level of detail[A]	Notes
EU	EMA	See **Table 6**		11	See Table 6
USA	FDA	Searchable Database (as per FDASIA)	Human MP that is life supporting/ life sustaining[11]	15	Applications for mobile phones also available
Canada	Health Canada	Shortage overview on website; details for each MP	Human MP	15	Website is not controlled by Health Canada, not legally binding
Australia	TGA	Searchable Database (criteria defines in the Specification are included[28])	Human MP	20	n / a

[A] see Annex II for evaluation matrix, and Figure 3 for a summary

II.B.3. Summary

Public DS reporting systems present on regulatory body websites for the EU, USA, Canada, and Australia were assessed with the types of reporting systems, the scope of reported pharmaceuticals, and the level of detail of information.

Overall, 32 categories of information were identified that could have been applied to the DS reporting system (compare Annex II). Figure 3 shows the calculated scores of all analyzed countries.

In total, 18 reporting systems were analyzed and a range from 7 - 20 points out of 32 was calculated.
The majority of reporting systems show low (8/18) to medium (7/18) granularity of published information, while only 3/18 reporting systems show high granularity. The leading regulatory agencies EMA, FDA, Health Canada and TGA were found to be as heterogeneous as the NCA in the EU (Figure 3).

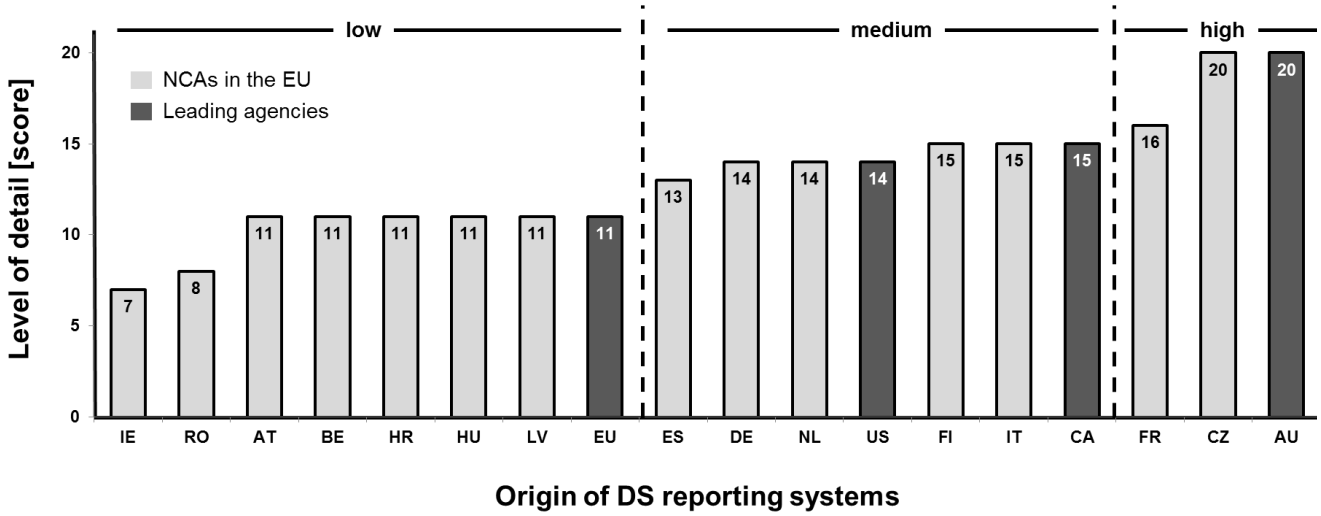


Figure 3 Details of information presented in DS reporting systems on official regulatory websites

Reporting systems have been scanned for the degree of publicly available information on DS. Granularity of information in 8/18 reporting systems was low, 7/18 was medium and 3/18 was high. Published categories of the reporting systems were compared and calculated using a detailed evaluation matrix (Annex II). The accessed websites can be found in Annex I. Level of detail: low: score 7-11.5; medium: score: 11.5-15.5; high: 15.5-20.

In principle, 4 different types of DS reporting systems on the website were found. 5/18 examined websites ran a searchable database, again 5/18 ran a shortage list on their website, and 6/18 allowed the download of a table in PDF or Excel format, while 2/18 presented DS information within other reports.

A correlation between the type of shortage and the level of detail of information is shown in Figure 4.
This analysis shows a correlation between the type of reporting system and the level of detail. The websites with the highest mean score (15.8) present DS information in searchable databases and the second highest mean score (13.8) correlates with shortage lists on the website. However, the median score of both types of DS reporting systems is similar (14 vs. 15). In contrast, websites with the lowest mean score (7.5) present DS information only within other reports. This indicates that a well-structured and organized DS reporting system is important for the users to easily and rapidly find that information they need.

Essentially, this analysis discovered that the landscape of public DS reporting systems is diverse. A good combination would be an easily accessible website with detailed information on DS that can be received by the users on request in a level of detail they prefer.

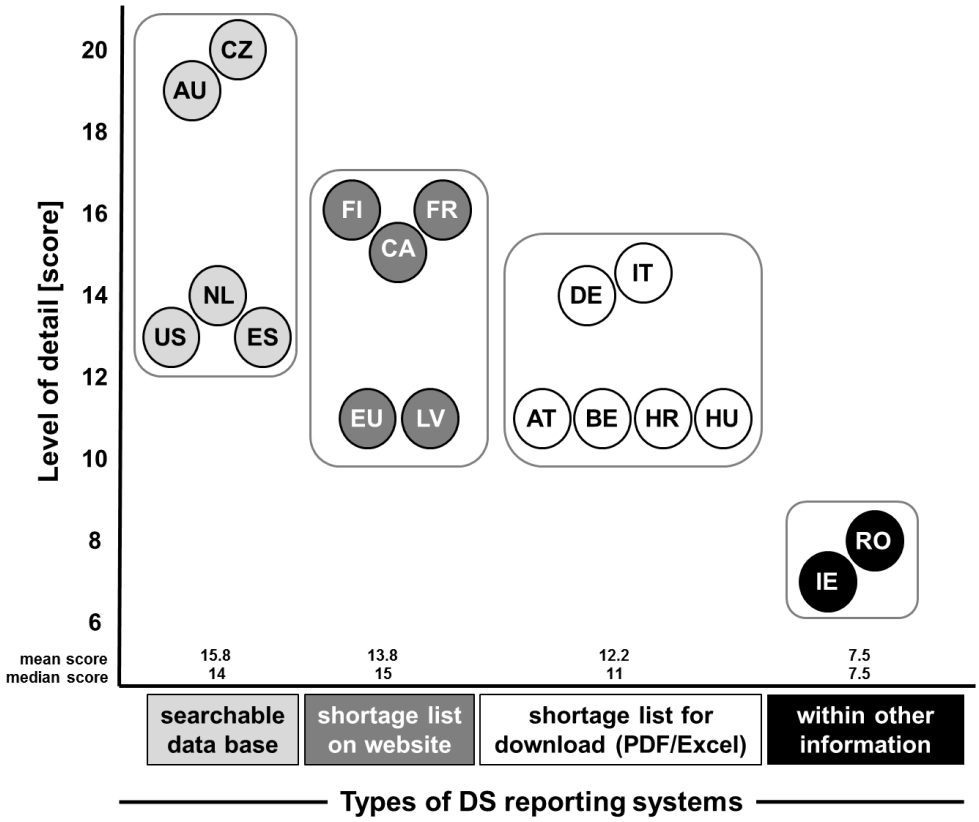


Figure 4 Types of DS reporting systems in correlation to the level of details on DS

18 websites were accessed (Annex I); the types of DS reporting systems were analyzed. The scores are taken from a previous analysis (Figure 3). This analysis shows a correlation between the amount of information published on the website and the structure and organization of the website.

III. MANAGEMENT AND COPING STRATEGIES

The data on public DS reporting systems provide valuable knowledge not only for therapy and treatment decision of pharmacists and HCP but also for patients. Therefore, this data are required to be up-to-date, trustful and comprehensible. This can be guaranteed only by following a management strategy that contains a structured assessment and coordinated roles and actions of the stakeholder.

In Chapter II, the availability of information about DS was discussed. Here, the development and implementation of different management strategies is examined (Chapter III.A). However, exclusively official, authorized approaches such as by regulatory bodies or the ministry of health are considered for the analysis. Furthermore, currently available management procedures are examined regarding their impact on improving DS situations in these countries (Chapter I.A.)

III.A. Development and mechanism of implemented of strategies

This Chapter describes the historical development of different tools, guidance documents, and approaches to cope with DS situations. In addition, the implementation and enhancement of different management strategies in the European Union, the United States of America, Canada, and Australia are examined.

III.A.1. European Union

Information on DS that affects or is likely to affect more than one EU Member State is published by EMA on the EMA website in a public catalogue of shortages[31]. It contains information about DS that has been assessed by EMA, and provides recommendations to patients and healthcare professionals across the EU. However, the shortage catalogue does not give a complete overview of all DS occurring in the EU, and there may be medicines in short supply that are not listed as most DS are dealt with at a national level[31]. Hence, EMA strongly advises to consults NCAs if additional information about the situation in a specific country is required[31] (see also Subchapter National crisis management).

In September 1997 the EMA crisis management plan for CAPs became effective[46]. Until 2009 the initial crisis management plan was revised and the scope was broadened to products registered via the national, mutual recognition or decentralized procedure to enable a more global approach[42]. Consequently, an *EU Regulatory Network Incident Management Plan* (IMP) for human MPs had been developed in relation to the management of incidents to avoid development into a crisis situation[41]. From 2009 to 2012 a pilot phase with the IMP was successfully started and is still valid today[41,46]. The key steps of the IMP are shown in Figure 5.

The IMP follows a two-step approach (proactive and reactive management) and consists of the three phases 1) *incident management phase*, 2) *trigger phase*, and 3) *crisis management phase*.

The key activity during the *incident manage phase* is the continuous monitoring of incidences by the established virtual *EU Incident Review Network (IRN)*. Various sources of information (e.g. social media, published data in journals, lay press, press-releases, and safety data at NCA) are considered actively. The collected information is rapidly exchanged with the NCA, the EMA, and the EC via appropriate communication channels (e.g. Rapid Alert for safety concerns, Non-Urgent-Information system for non-RAs). In addition, the information are accessed via the *European Pharmacovigilance Issues Tracking Tool* (EPITT) to which also members of the CHMP, PRAC, CMD(h) have access. Notably, for quality concerns that do not affect safety there is another procedure available and the IMP is not used[60].
Once the information on incidents is distributed, the IRN reviews the incidents from a managerial point of view and identifies the legal and regulatory framework. Finally, the IRN evaluates the incidents to identify a potential crisis situation (Figure 5, part 1) and proposes options to manage the DS situation[41].

The proclamation of a potential crisis situation by the IRN triggers the involvement of the *EU Executive Task Force* (*triggering phase*). In this case, a preliminary risk analysis is requested from EMA (in collaboration with CHMP/PRAC) or RMS/lead MS depending on the licensing route of the concerned MP. In order to allow for an efficient and rapid decision-making, the IRN provides an adapted timeframe for the preparation of the PRA. The final PRA is than send to the EU Executive Task Force for review and decision, and confirmation of a crisis situation (Figure 5, part 2) [41].

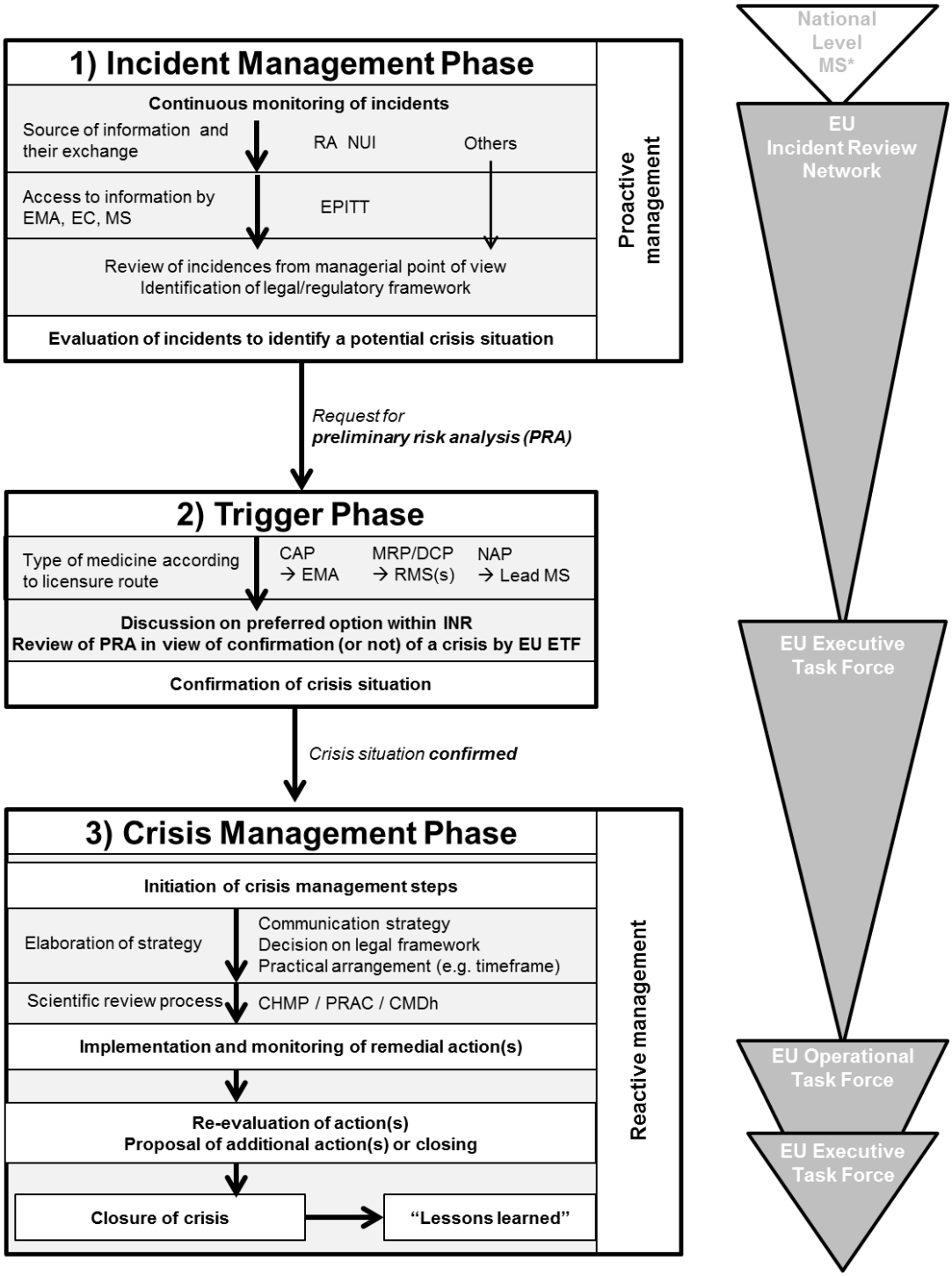
After a crisis situation is confirmed, the *crisis management phase* begins with the reactive management of the DS situation (Figure 5, part 3)[41]. First, the EU Executive Task Force decides on the basis of the PRA if all or only parts of the crisis management steps proposed by the IRN are initiated. Moreover, management strategies regarding the communication strategy, legal framework, and shortest possible timeframe is elaborated. Subsequently, the *EU Operational Task Force* implements the decisions and operates the crisis management steps within the agreed timeframe. The implemented actions are monitored and re-monitored by the EU Operational Task Force in order to propose additional actions or closing of the crisis situation. All proposals are reviewed and decided by the EU Executive Task Force[41].
The crisis situation will be considered closed once the EU Executive Task Force on the basis of advice provided by the EU Operational Task Force has agreed upon such closure. Then, a close out letter will be sent by the EMA on behalf of the EU Executive Task Force to all involved parties. Finally, after each crisis, the EU Executive Task Force initiates a *lessons learned session* (Figure 5, part 3)[41].

In summary, the IMP is flexible enough to address the various situations which may arise in the complex EU regulatory framework, not only regarding DS situations, and to take due

account of its specificities. In only a few situations, the entire IMP needs to be followed, and for most situations the incident management steps are applied[41].
Beside the IMP that was developed in 2009, further tools were developed to guide MAHs, patients and NCA during DS situations.

In 2013, a public workshop on DS due to manufacturing and quality problems was conducted at EMA[43,61]. In this workshop an inter-association task force was established that defined an implementation plan to establish additional tools and documents to improve the management of DS situations at EU level and national level[43,61].
In total seven additional tools have been implemented: 1) criteria for classification of critical medicines[36], 2) a defined common assessment report for benefit-risk assessment[62], 3) a protocol for the overall assessment of a DS due to manufacturing problems[63], 4) a guidance for the identification of risk indicators for DS[61], 5) a decision tree to assist the decision whether a national DS should be escalated to EU level[37], 6) information sources issuing treatment recommendations during DS[64], and 7) a public catalogue of DS[31].

During a stakeholder meeting on October 9, 2015, the progress made since implementation of these documents was reviewed and discussed[44,61].
In summary, the work done so far to cope with DS was encouraging, but DS continue to impact patients care and hence, further effort is needed to more proactively avert DS and reduce their impact[44,61].



* see National crisis management for more information

Figure 5 European Incidence Management Plan

This flowchart is modified from *the European Union regulatory network incident management plan for medicines for human use*[41]. The Incidence Management Plan consists of three phases and can be triggered by EMA, NCA and the European Commission.

a) National crisis management

It is the responsibility of each NCA to establish a national crisis management structure that allows for adequate interaction with the management structures set-up at EU level[41]. Such national structure should operate in accordance with a national crisis management procedure. Any application of the IMP fully acknowledges the rights of the NCAs to take pre-emptive action at national level in accordance with the provisions of EU legislation[41]. While there is a management plan available from EMA, the management procedures at the NCA in the MS are mainly elusive.

In Germany, a regular meeting with the NCA BfArM and PEI, and stakeholders from industry was established recently to discuss and improve the DS situation. On September 08, 2016 the first meeting was conducted[91].
Currently, there is no requirement for a manufacturer or MAHs to notify the NCA of a potential DS in Germany but a voluntary notification system is available. BfArM and PEI receive shortage information and perform a risk assessment to evaluate if critical pharmaceuticals are involved and if a DS situation or stock-out situation is present[91]. The establishment of an early notification system to identify potential DS is an important goal of BfArM; however, this is not a solution for underlying problems. The use of this notification system was by who and how discussed and the staggered approach of PEI to publish information on DS situations was judged as being valuable. Furthermore, acknowledgement in the first meeting pushed for multi-layered, remedial, actions that need to be addressed with various stakeholders[91].

As a first reaction towards increasing DS situation, the German Drug Law (Arzneimittelgesetz, AMG) has been amended recently[104]. Herewith, the national authorities are authorized to inform health care professionals about the number and dosages of released batches of pharmaceuticals that are available for use. In particular, this information is valuable for health care associations, such as the STIKO (Ständige Impfkommision) to give guidance on treatment or vaccination recommendations in case of DS situations.

III.A.2. United States of America

In response to a dramatic increase in shortages the *Executive Order 13588* was issued in the US recognizing that "…shortages of pharmaceuticals pose a serious and growing threat to public health […] and increase health care costs"[51,52]. The Executive Order directed FDA to take steps to help prevent and reduce current and future disruptions in the supply of lifesaving medicines, through notifications and expedited reviews, as appropriate[51,52].

On July 9, 2012 *The Food and Drug Administration Safety and Innovation Act* (FDASIA) was enacted amending the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) by updating section 506C[7-15]. With the passage of FDASIA, FDA was given important new authorities related to DS such as early notification provisions[10,11], noncompliance letter to firms that fail to notify FDA[7-10], expediting reviews of pharmaceutical/supplemental applications and inspections that could help mitigate a shortage[51]. Other FDASIA

requirements include improving FDA's internal and external communications about shortages and developing a strategic plan to enhance FDA's response to preventing and mitigating DS[51].
For details regarding the legal requirements and responsibilities, see Chapter I.D.

Current processes applied by FDA to manage DS are transparently communicated. DS of biological MP are managed by the CBER and DS of other pharmaceuticals than biologics by the CDER. For CDER-regulated MP, processes to manage DS are explicitly described in the current *Manual of Policies and Procedures*[38], and processes regarding shortages of CBER-regulated MP are described in the current *Standard Operating Policy and Procedure*[39], respectively.

A flow chart showing established procedures for notification, evaluation, and management of DS situations for all CDER products[6] is shown in Figure 6.

[6] This work focusses on CDER-regulated MP. However, the procedures established at the CBER are found to be similar.

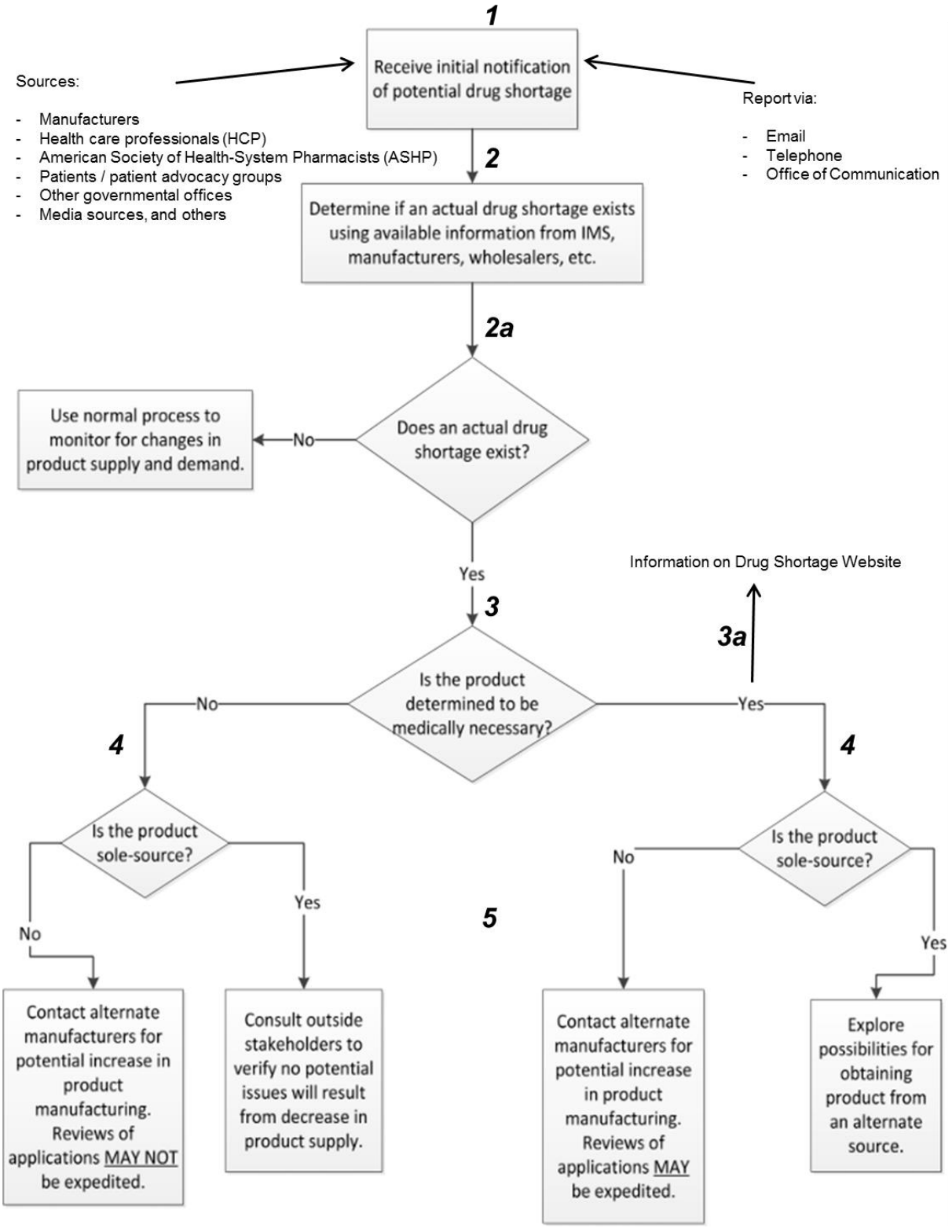


Figure 6 DS Processes coordinated and initiated by the Drug Shortage Staff at CDER / FDA

Modified for the use within in this work. Taken from CDER MAPP (2014)[38].

For DS management, the position of Drug Shortage Staff (DSS) at CDER was applied[38]. The DSS has a network of designated contacts within CDER to address pharmaceutical availability issues comprehensively and proactively. It monitors pharmaceutical supply and demand to ensure availability for emergency situations, and serves as a liaison to private industry, other FDA centers, and other government organizations[38].

First, the DSS receives and evaluates information regarding potential or actual DS (Figure 6, step 1). Notably, notification is legally binding only for manufacturers of life supporting / sustaining prescription MP likely to lead to a meaningful disruption in supply (Chapter I.D.2), but the FDA also appreciates and evaluates early notification by FDA offices, external entities, and additional sources[38]. The established procedures apply not only to marketed products but also to investigational new pharmaceuticals[38]. Information to be supplied to FDA should include the requirements set out in CFR, title 21, §314.81 to assist FDAs rapid response[40] (Chapter I.D.2). Applicants should notify FDA electronically in a format FDA can process, review, and archive. So far, email notifications will be used but in future the Agency may consider creating an electronic notification portal linked to the Agency's internal DS database to facilitate submission of these notifications and report the DS case[40].

Second, DSS verifies if an actual DS exists (Figure 6, step 2). Therefore, the DSS uses different tools to systematically collect information to accurately assess the DS situation. The following criteria are applied: current and historic product demands, available stocks, manufacturing schedules, and product distribution at wholesale levels. Furthermore, the DSS evaluates this information in detail to confirm that a DS actually exists (Figure 6, step 2a).

Third, if needed, the DSS requests a new or updated *Medical Necessity Determination form* from the division with the respective expertise on that MP (Figure 6, step 3). It is important to note that the definition of *medically necessary* in the MAPP differs from FDA's definition of *life supporting* or *life sustaining.* In general, FDA considers a product to be medically necessary if there is no other product that is an appropriate substitute or there is an inadequate supply of an acceptable alternative. This is to prioritize the Agency's response to specific or potential shortages and to allocate resources appropriately. Appropriate CDER medical officers familiar with the concerned MP are responsible for judgement[38]. When the DSS has confirmed an actual DS of a medically necessary MP exists, the DSS will post this information on the Drug Shortage Website[38] (Figure 6, step 3a).

Fourth, depending on the numbers of manufacturers of the concerned MP, a strategy to resolve the DS is determined (Figure 6, step 4). In case an alternate manufacturer is available, DS contacts the alternate manufacturer for the potential increase of manufacturing the product; otherwise, if no other manufacturer is available, DSS explore possibilities for obtaining product from an alternate source. This may be also facilitated by expediting review of applications (Figure 6, step 5 right) [38].

The entire procedure is well-structured and coordinated by DSS and all FDA subdivisions are orchestrated allowing a close collaboration and fast reaction.

III.A.3. Canada

Due to a dramatic increase of DS in 2010 and 2011, the Minister of Health called on industry to voluntarily provide public notification of DS. In response, a web-based voluntary notification system was created in 2012 and continued to operate by industry associations[16]. Prior to 2012, no reporting system for DS or discontinuations existed in Canada. Despite some improvements in industry notification, there have been persistent challenges with the voluntary approach, as some companies did not file DS notification or not in a timely fashion[53]. Still, the lack of timely, complete, and accurate information poses potential health and safety risks for patients and additionally creates labor for pharmacists and HCP[16].

In 2012, the *Multi-Stakeholder Steering Committee on Drug Shortages* (MSSC) was assembled in 2012 with representatives of industry associations, federal, provincial and territorial governments, and health professional associations.

In 2013, the MSSC created two important resources for understanding and mitigating DS in Canada: 1) the *MSSC Multi-Stakeholder Toolkit* describing the Canadian drug supply chain, clarifies roles and responsibilities, and identifies tools and strategies to address DS[54] and 2) the *Protocol for the Notification and Communication of Drug Shortages*, setting out clear expectations for the notification and communication of information in anticipation of or in response to a DS[48].
Both, the Toolkit and Protocol, have been establish to provide common understanding and expectations to support coordinated multi-stakeholder communication and engagement to counteract, mitigate and manage DS in Canada.

For the notification and communication of information in response to a DS a tiered process was established (Figure 7, *Tiered Notification and Communication Framework)*[48].
Based on pre-determined criteria (anticipated DS, actual DS with and without therapeutic alternatives), each tier provides the requirements for notification and communication and identifies clear responsibilities and roles of the stakeholders (Figure 7, Tier 1-3). However, it provides a flexible structure that can be tailored to the specific characteristics of each DS.
In every case of DS, notification involves the posting of DS information on the website by manufacturers and importers since this should build the foundation of collaborative and informed response on DS[48].
Notably, the multi-stakeholder approach is different from the approaches in the USA and EU. In Canada, the regulatory authority is not heading the processes to the same extend than in the EU or USA. While NCA/EMA and FDA are heading management processes, Health Canada has a supportive, non-leading role (Figure 7, Tier 2 and 3, Federal Health Portfolio).

Tier 1: ANTICIPATED DS

Manufacturer(s) will:
- Post up-to-date, comprehensive drug shortage details to www.drugshortages.ca
- In addition:
  - Collaborate with stakeholders across supply chain and validate comprehensive drug shortage details
  - Provide early notice to stakeholders to emerging shortages of concern

P/T Health Ministries, Regional Health Authorities, Hospitals, and Federal Drug Plans:
- Confirm/assess shortage specifics in consultation with relevant stakeholders including hospitals pharmacies, manufacturers, GPOs, distributors and wholesalers
- Provide regular and ongoing communication of shortage details to local healthcare delivery stakeholders

GPOs, Distributors, Wholesalers, Community Pharmacies and Healthcare Professionals:
- Collaborate with stakeholders across supply chain to share and confirm comprehensive drug shortage details by monitoring stock levels and providing regular and ongoing communication of the shortage details at the local, regional, provincial or territorial level

Tier 2: ACTUAL DS

Manufacturer(s) will:
- Post up-to-date, comprehensive drug shortage details to www.drugshortages.ca
- In addition:
  - Collaborate with stakeholders across supply chain and validate comprehensive drug shortage details, including detailed information on mitigation measures, and drug supply, allocation, distribution and return to market dates
  - Provide early notice to stakeholders of emerging shortages of concern
  - Notify P/T Drug Shortage Task Team of all actual drug shortages

P/T Drug Shortage Task Team:
- Coordinate communications with F/P/T Health Ministries, Regional Health Authorities, Federal Drug Plans, and Manufacturers to confirm/assess status and details of shortage (including tier 2 and 3 criteria)
- Notify Health Canada in the event shortage is deemed to meet Tier 3 criteria

Federal Health Portfolio (Health Canada):
- Participate in communications between manufacturers and P/T Drug Shortage Task Team to assess details and status of drug shortage
- Liaise with P/T Drug Shortage Task Team Chair

P/T Health Ministries, Regional Health Authorities, Hospitals, and Federal Drug Plans:
- Confirm/assess shortage specifics in consultation with relevant stakeholders including hospital pharmacies, manufacturers, GPOs, distributors and wholesalers
- Provide regular and ongoing communication of shortage details to local healthcare delivery stakeholders

GPOs, Distributors, Wholesalers, Community Pharmacies and Healthcare Professionals:
- Collaborate with stakeholders across supply chain to share and confirm drug shortage details
- Communicate allocation and distribution information, as needed

► see next page for Tier 3.

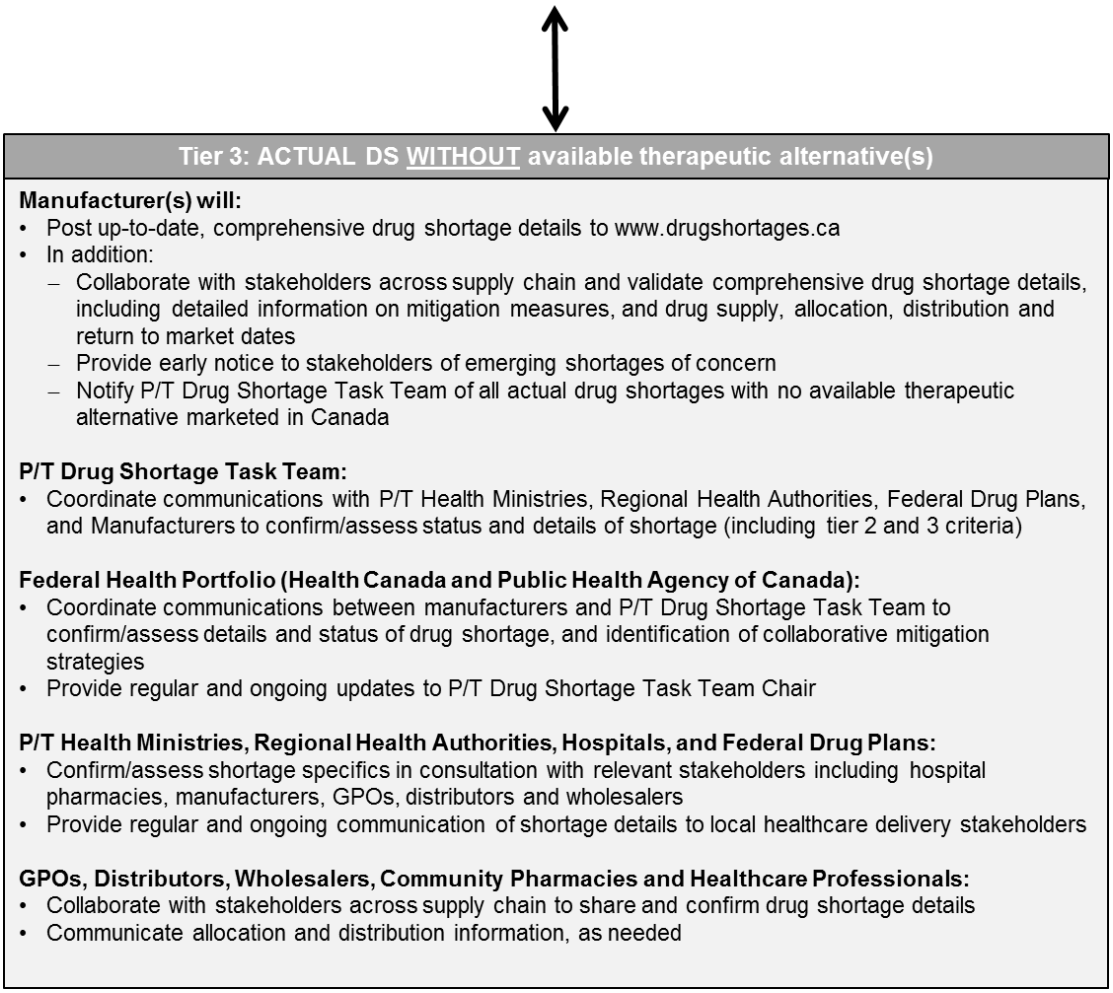


Figure 7 The Tiered Notification and Communication Framework in Canada

Figure is taken from the Protocol for the Notification and Communication of DS[48].

In February 2015 the Canadian Minister of Health announced that public reporting of DS and discontinuations will become mandatory as the voluntary procedure is ineffective and puts patient safety at risk[19]. Therefore, amendments of the Food and Drug Regulations were enacted, coming into effect in spring 2017[19].

In principle, the procedures required under the new regulation are in accordance with the voluntary multi-stakeholder procedures presented above. Statutory amendments include definitions of the term *DS* and *discontinuation*[21,49], mandatory notification of DS and discontinuations by the authorization holder; mandatory reporting to a website that is operated by an authorized party for that purpose[20,49], and timelines required for notification depending on the characteristic of the DS[22,49].

According to the tired multi-stakeholder approach presented in Figure 7, a schematic overview of the requirements of the new amendment coming into effect in spring 2017 is shown in Figure 8. Again, Health Canada does not have a leading role, but plays an active role as federal regulator.

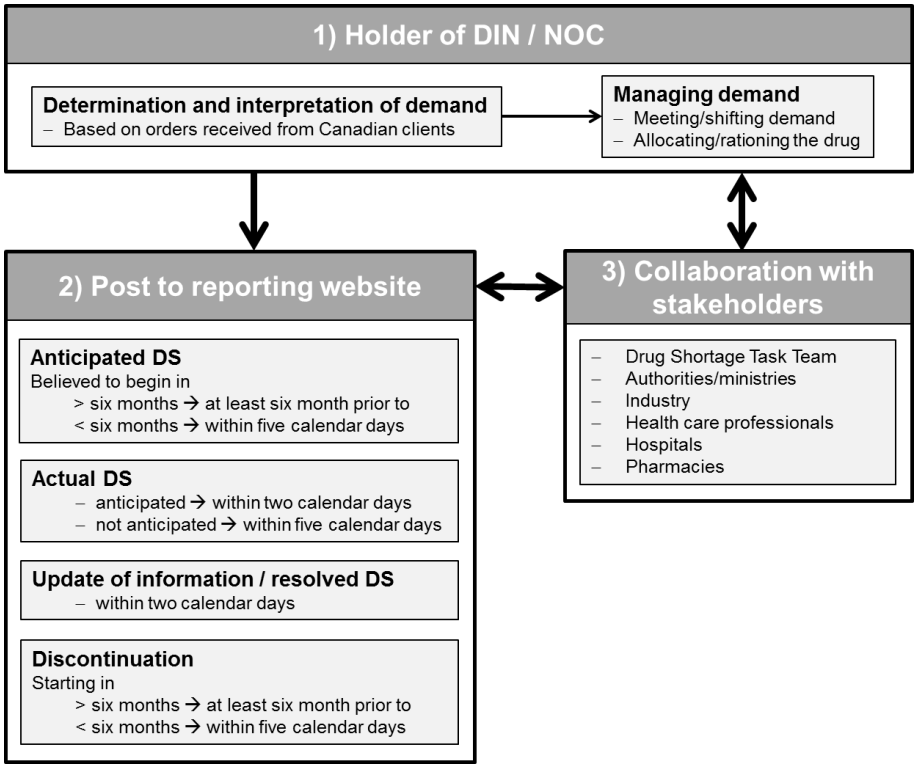


Figure 8 Overview of requirements within the Tiered Notification and Communication Framework

The mandatory notification and reporting procedure described in the Regulations Amending the Food and Drug Regulations[19] will come into effect in spring 2017[49]. Then, authorization holders are required to report any DS to the respective report website within a defined period. The DS management is a multi-stakeholder process (see Figure 7 for details).

III.A.4. Australia

In Australia, the *Medicine Shortages Information Initiative* was founded to provide information about prescription DS in Australia and to assist HCP and consumers when there is a temporary or permanent disruption (discontinuation) to the supply of a medicine[55]. The initiative has the goal of improving the communication and management of DS and is led by a partnership between the TGA, Medicines Australia and Generic and Biosimilar Medicines Association[50]. It includes a website, hosted by the TGA, where information about the nature, anticipated duration and status of prescription DS are published[55,56,57]. Interestingly, this initiative is not designed to prevent DS from occurring[57].

In 2014, the Initiative published a Protocol[50] as a guidance document for Australian Sponsors and the TGA regarding the communication and management of DS. It describes the roles of the stakeholders, the sponsor and the TGA in the communication and management of DS, and features the principles of 1) timely notification regarding DS, 2) structured assessment of DS, and 3) coordinated response and communication. However, the Protocol does not alter

or replace current responsibilities of parties in managing DS[50]. The general principles of the Protocol[50] are shown in Figure 9.

All sponsors should act proactively against DS by accurate demand forecasting, maintenance of appropriate levels if safety-stocks and identification of back-up supply routes (Figure 9, step 1). When the sponsor becomes aware of a DS or anticipates a DS he should assess the level of impact to consumers using the assessment framework as defined in the Protocol[50](Figure 9, step 2). Depending on the outcome of the assessment, the sponsor should develop and implement strategies to communicate and resolve the DS situation (Figure 9, step 3). The output of the assessment is assigning a high, medium, or low impact level. This level defines a graduated set of required response activities. This can be done in cooperation with the TGA to achieve the most efficient communication and a rapid coordinated response[50] and it includes the steps from notification, assessment/response to reporting/publication and update of information[50].

Figure 10 shows the activities by shortage type that sponsors and the TGA should perform.

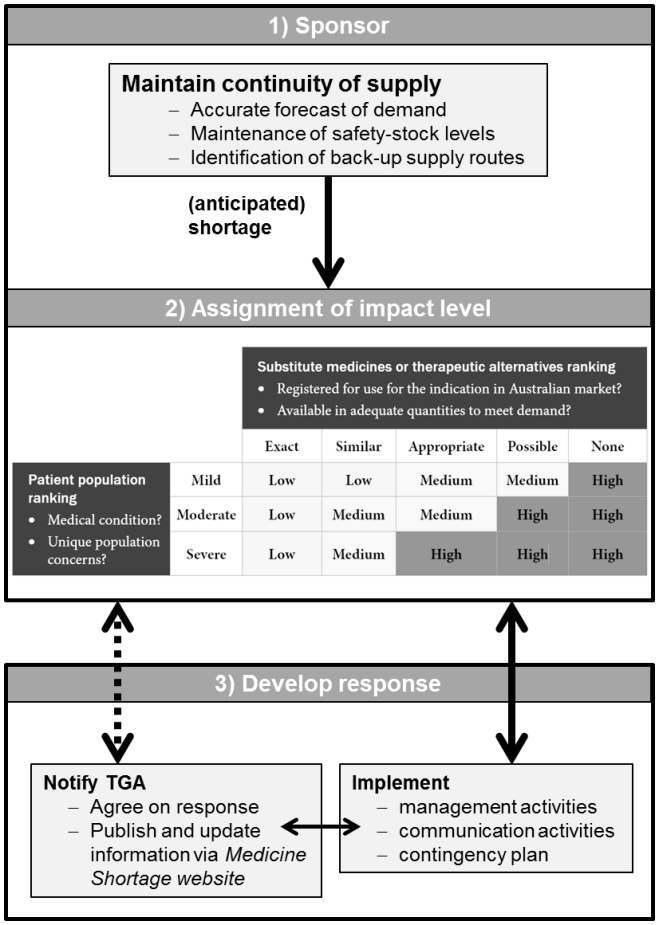


Figure 9 General principles of the Protocol for Australian Sponsors and the TGA

This flowchart was developed according to the *Protocol for Australian Sponsors and the TGA*[50]. It highlights the particular actions a sponsor is recommended to conduct in order to resolve DS as rapidly as possible. The assignment of impact level is done by the sponsor and other stakeholder such as the TGA allowing a flexible case-by-case approach to resolve DS.

Shortage types	Activity steps		
	1. NOTIFY		
Anticipated shortages	Yes		
Current shortages	Yes		
Discontinuations	Yes		
	2a. ASSESS		
Anticipated shortages	Yes		
Current shortages	Yes		
Discontinuations	Yes		
	2b. RESPOND		
Anticipated shortages	HIGH Yes Public health escalation	MEDIUM Optional	LOW Optional
Current shortages	HIGH Yes Public health escalation	MEDIUM Yes	LOW Optional
Discontinuations	HIGH Yes Public health escalation	MEDIUM Yes	LOW Optional
	3. PUBLISH		
Anticipated shortages	HIGH Yes With information about supply arrangements for substitute medicines or therapeutic alternatives linked to website, as appropriate	MEDIUM Optional	LOW Optional
Current shortages	HIGH Yes With information about supply arrangements for substitute medicines or therapeutic alternatives linked to website, as appropriate	MEDIUM Yes With information about supply arrangements for substitute medicines or therapeutic alternatives linked to website, as appropriate	LOW Yes
Discontinuations	HIGH Yes With information about supply arrangements for substitute medicines or therapeutic alternatives linked to website, as appropriate	MEDIUM Yes With information about supply arrangements for substitute medicines or therapeutic alternatives linked to website, as appropriate	LOW Yes
	4. UPDATE (Noting that the information in the update may result in a different impact level and hence response plan)		
Anticipated shortages	YES regardless of impact level		
Current shortages	YES regardless of impact level		
Discontinuations	YES regardless of impact level		

Figure 10 Activities by shortage types

Figure is taken from the *Protocol for Australian Sponsors and the TGA*[50]

In Australia, there is no provision in the legislation that requires sponsors or the TGA to take actions when a DS occurs or is anticipated. Furthermore, unlike in Canada (compare III.B.3) it is not planned to change this regulation.
The management of DS in Australia is a multi-stakeholder approach where the sponsor has a central and the TGA a cooperating role. When a DS is notified to the TGA, the sponsor will normally initiate the process of assessing the impact and considering the appropriate activities for communicating to the stakeholders within the supply chain[50].
Information regarding DS will normally be published with the consent of the sponsor. However, TGA is able to publish information about DS under a legislative instrument under section 61 of the Therapeutic Goods Act (compare I.D.4) which provides the TGA with authority to release information to the website regardless of this consent[29].

III.A.5. Summary

In this Chapter different approaches and strategies to manage DS were described. An overview of DS management strategies is summarized in Table 8.

In the EU, DS are mainly within the responsibility of each member state; however, the EU-wide Incident Management Plan was implemented to cope with DS that affect more than one MS.
In the US, the provisions of FDASIA changed the landscape of DS management from no regulation to mandatory procedures handing over more legal power to FDA. At FDA the Drug Shortage Staff was established to secure appropriate DS management including rapid notification, reporting, and communication.
In Canada and Australia, no provisions regulating DS management are currently available. A multi-stakeholder guidance is available for both countries defining the roles of the various stakeholders, including regulatory bodies, in a DS situation. In spring 2017, provisions will come into effect in Canada that tightly regulates the multi-stakeholder approach in managing DS situations. Yet, this is not planned for Australia.

Essentially, there is no common approach of managing DS situation in all countries, but yet the three pillars *notification as early as possible*, *structured assessment*, and *coordinated responses* seem to be the most crucial factors for reducing impact on patients and resolving the DS situation.

Table 8 Comparison of DS management strategies in the EU, the US, Canada, and Australia

Criteria	European Union	United States of America	Canada	Australia
Trigger of initiating DS management processes	Various	Various	Mainly holder of DIN/NOC	Mainly sponsor
Assessment of - critical pharmaceutical(s) - impact on patients - anticipated/actual DS - alternative therapies	 Yes Yes Yes Yes	 Yes Yes Yes Yes	 No No Yes Yes	 Yes Yes Yes Yes
DS notification to regulatory body **-** required by law - timely defined - anticipated/actual - via - standardized notification form	 - No - No - Actual[7] - Email - Yes	 - Yes - Yes - Anticipated/actual - Email, telephone - No	 - No (yes)[8] - No (yes) - Anticipated/actual - Post on website - No	 - No - No - Anticipated/actual - Email, telephone - No
Role of regulatory body	Leading	Leading	Supporting	Supporting
Reporting website: - hosted by - post is mandatory - post done by - reliable source of information	 - EMA - No - EMA - different for EMA/NCA	 - FDA - Yes - FDA - Yes	 - Third party[9] - Yes, - DIN/NOC holder - Yes, mostly	 - TGA[10] - No - Sponsor/TGA - Yes, mostly
Types of pharmaceuticals listed on reporting website	EMA: Critical pharmaceuticals when more than one MS concerned NCA: different	Lifesaving/-sustaining pharmaceuticals, intended for use in prevention / treatment of a debilitating disease/condition	All	All prescription drugs on the Australian Register of Therapeutic Goods
Management of DS	Proactive and reactive in equal parts	Proactive and reactive in equal parts	Less proactive, more reactive	Less proactive, more reactive

7 According to Reference[59] potential DS should be published, but category is not presented in shortage catalogue.
8 Mandatory when new regulations come into effect (spring 2017).
9 Hosted by industry-led parties. When new regulations come into effect a Third party is authorized for hosting.
10 Hosted by TGA but not in responsibility of TGA.

III.B. Evaluation of implemented strategies

The development and establishment of DS management strategies were described before (Chapter III.A).

Here, implemented tools and approaches are evaluated in order to determine their benefit in managing DS situations in the European Union, United States of America, Canada, and Australia. In the end, a comparison between the different countries is done (Chapter III.A.5).

III.B.1. European Union

In 2009, the Incident Management Plan (Figure 5) was developed to prevent crisis situations in the EU that originate from DS[41]. Since 2013, a set of guiding documents is available to support regulators at national competent authorities with the management of DS situation due to GMP non-compliance/quality defects[36,37,42,43] (Chapter III.A.1).

EMA representatives conducted a survey amongst MS in the EU in August 2015 to re-evaluate the progress of DS management after the implementation of the IMP and the guiding documents[44,45].
In summary, the results of the survey showed that, although there is no harmonized assessment and approach to reporting and dealing with shortages, common points were identified. The survey found that mandatory notification for shortages was a requirement for most MS (21/28 that responded to the survey) and that the information required by individual MS is similar and partially overlapping, although there is no EU-wide template for notifications. Furthermore, it was shown that there is no common definition of *drug shortage* being an obstacle for the benchmarking of management approaches[44,45].

The extent of information about DS that were published on the website of the NCA during the EMA survey in 2015 were compared with the finding in this in this Master's Thesis (data from Chapter II.B.1 and Annex II). The presence of information regarding the reasons of DS, the estimated start and end of the DS, alternative treatment recommendations as well as communication/mitigation plans were compared. The comparison is shown in Figure 11.

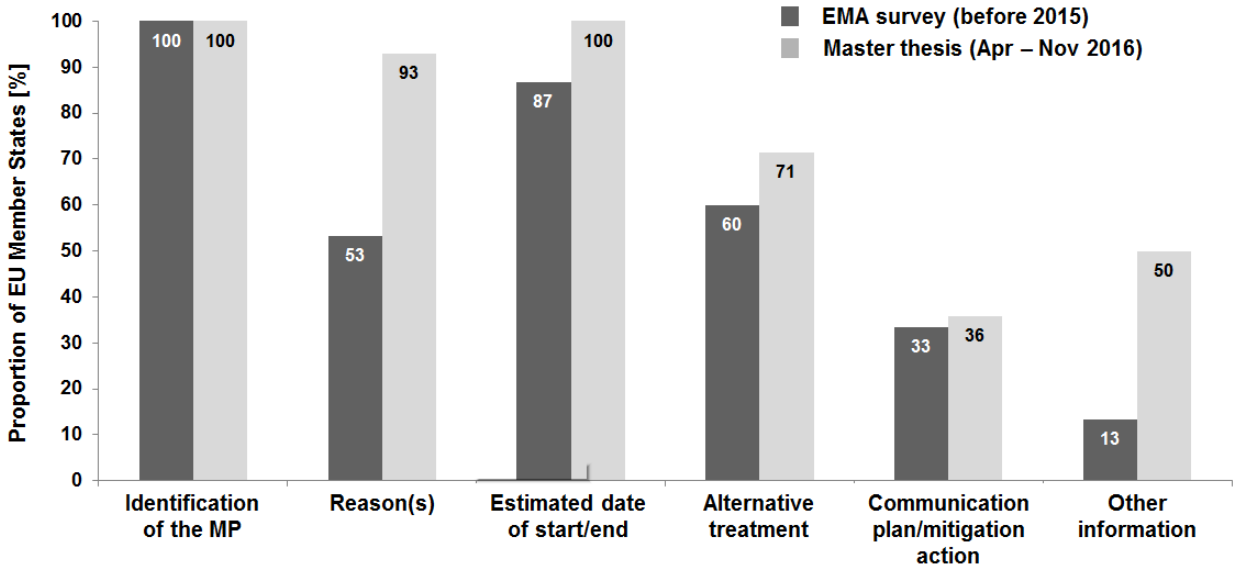


Figure 11 Re-evaluation of the progress of DS management on EU level

Data are taken from question 4b of the EMA Survey[45] that were presented on the stakeholder workshop at EMA in 2015[44]. The percentages were calculated using the collected data presented in Annex II. The category "identification of the MP" served as basis for the calculation (100%) because it represents the minimal requirement for reporting. The categories "stock available (units)" and "monthly sales of the affected MP" in the EMA survey were are not shown because these have not been assessed in this Master's Thesis.

More information about DS is published on the websites of NCA in 2016 compared to 2015. Only half of the MS that participated in the EMA survey did publish the reasons for the occurring DS on their website (53%), while the number in 2016 almost doubled (93%). Interestingly, the amount of websites publishing information on communication plans and mitigation strategies during DS (33% vs. 38%) did not increase as significantly as all the other categories. This might indicate that MS are lacking efficient communication plans or that each DS is unique and needs an individual communication and mitigation strategy.

While this comparison suggests that the implemented IMP and guiding documents improve the transparency of information on DS in the MS, the advantage of these approaches needs to be evaluated further. Hence, the EU has launched a European Medicines Shortages Research Network in 2016 to look at the causes of DS and their impact on patients[47].

In summary, this comparison shows that the EMA survey in 2015 and the data obtained in this work are similar. In the EU there is still not yet a common approach of assessing and managing DS; however, there are common concepts that could be developed into a best practice guide for DS in Europe. Moreover, it is questionable, whether a European regulation specifying the reporting and management requirements, as in the US or Canada (Chapter I.D.2 and I.D.3), should be favored.

III.B.2. United States of America

With the enactment of FDASIA several provisions were introduced to improve the DS situation in the US (Chapter III.A.1.a)).

From 2012 when FDASIA was enacted, until 2015, the number of new shortages significantly decreased (Figure 12, dark gray bars). While there have been identified 117 new cases of DS in 2012, only 22 new cases of DS occurred in 2015. Although the number of new cases was decreasing, the number of prevented DS cases was similar in 2013 (170), 2014 (101), and 2015 (128; Q3) (Figure 12 light gray bar). In addition, FDA identified 97 ongoing or persistent DS at the end 2013 and 74 ongoing DS at the end of 2014. As of September 30, 2015, there were 48 ongoing DS[51]. Essentially, less new cases of DS occurred in 2015, while equal numbers of DS were prevented by FDA.

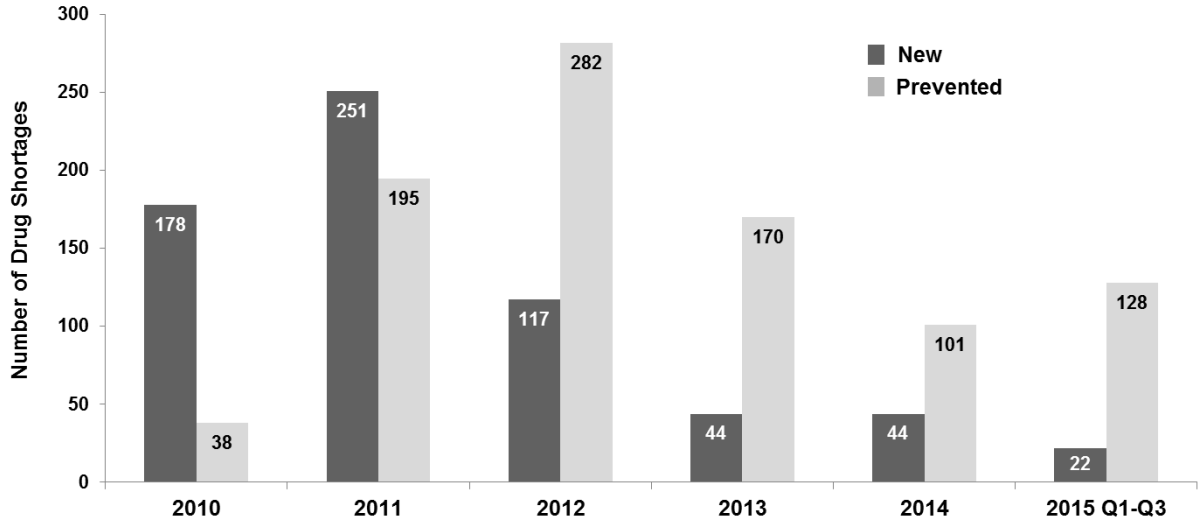


Figure 12 Number of new and prevented DS in the US

The data are evaluations from CDER's drug shortage database and taken from the Third Annual Report on Drug Shortages for Calendar Year 2015[51] and adapted for use in this Master's Thesis.

The searchable FDA Drug Shortage database website provides easy access to information about DS and remains a valuable resource to the public (>3.2 million page views until Q3 2015)[51]. Moreover, FDA launched its first mobile application in March 2015 which is an innovative tool providing easy and fast access to important real-time information about DS, especially for pharmacists and HCP making treatment decisions. As of September 30, 2015, there have been almost 22,000 installs of the Drug Shortage App[51].
Unfortunately, no data showing direct benefit of these tools are available yet.

FDASIA requires FDA to send a noncompliance letter to companies that fail to notify FDA of any DS[7-10]. No non-compliance letters were sent in 2015, while FDA sent two letters in 2014 and posted the letters and the responses from the manufacturers on its website[51].

In summary, this data indicate that the implemented provisions by FDASIA are effective for improving FDAs management of DS. However, a direct comparison to other countries with similar provisions is lacking to date, so that the advantages of the implemented provision is uncertain.

III.B.3. Canada

Currently, there is no provision requiring the mandatory notification and reporting of DS in Canada. Despite the establishment of the MSSC and the development of guidance documents, such as the MSSC Multi-Stakeholder Toolkit and the Protocol for the Notification and Communication of Drug Shortages (Chapter III.A.3**)**, there is persistent challenge with DS in Canada. Amendments of the Food and Drug Regulations coming into effect in spring 2017 will require mandatory notification within a specified period in order to better control and manage DS in Canada.

These provisions are similar to the one in the US. The approach involves multiple stakeholders but unlike the leading role of FDA in the US, the regulatory authority in Canada is equivalent to other stakeholders. Therefore, it will be interesting to compare the progress of improving the DS situation in both countries, the US and Canada.

III.B.4. Australia

Mandatory DS notifications are not required in Australia. A comprehensive protocol was established to guide sponsors and the TGA in case of DS; however, this procedure is voluntary only[50].
There is no official report available showing data about the DS situation in Australia and the success of the implemented Protocol. Approximately 80% of all Australian sponsors comply with the Protocol[30]. Referring to media, this results in delayed or partially incomplete information on the shortages website so that patients and HCP do not rely on the content[58].

III.B.5. Summary

In this Chapter, the success of implemented tools and approaches in order to resolve DS situations was evaluated. Different tools and mechanisms to identify and manage DS have been presented.
In general, it was found that once a DS situation occurs, the management is faster and easier when a structured and coordinated process comes into effect. Whether this process needs to be initiated by a higher regulatory body versus other stakeholders, such as the sponsor or manufacturer, is unclear. Furthermore, it remains elusive whether provisions in the legislation that regulate management processes are required for DS situations. Up to now, no reliable data is available showing the benefit of different DS management approaches.

IV. REGULATORY GOVERNANCE OF DS SITUATIONS

One of the top priorities of regulatory authorities is to guarantee the quality, safety, and efficacy of pharmaceuticals, and to assure the availability of new and innovative pharmaceuticals to patients.
The concept of communicating DS situation to various stakeholders in the healthcare system using a notification procedure and reporting system was already applied in many countries. This led to enhanced transparency and enabled earlier search for appropriate treatment alternatives; however, this still did not prevent DS from occurring[81]. Therefore, effective prevention and mitigation strategies are needed in addition to be prepared for upcoming DS situations.

Notably, very early stakeholders e.g. from industry developed potential recommendations for action for MAHs, manufacturers and suppliers to prevent and mitigate DS[92,95,96]. These should be considered as *best practice guides* for industry since they do not have a legal basis. In addition, there are also guidelines available that were developed together with regulatory authorities[93,94]. Yet, this diversity of proposed prevention and mitigation strategies shows that there is no uniform approach available for this global problem.

In this Chapter, potential approaches to prevent and mitigate DS through regulatory governance are presented (Chapter IV.A) and potential challenges are analyzed (Chapter IV.B).

IV.A. Regulatory prevention and mitigation strategies

DS are a globally experienced phenomenon since decades. The causes and relations underlying DS are varied and not easy to understand. All stakeholders in the healthcare system are tremendously impacted when a DS occurs; therefore resolution to end DS is urged. To end DS situations the underlying causes need to be eliminated; however presents a major challenge (Chapter I.C). The development of regulatory prevention and mitigation strategies for DS is primarily intended for the elimination of the DS itself and mostly does not eliminate the underlying causes. Roughly, underlying causes can be divided into economic / business driven causes and issues in manufacturing and supply chain[84].
This Chapter describes potential regulatory actions that can be implemented to prevent and mitigate DS. Various sources were analyzed to seek for potential prevention and mitigation strategies on a short to long-term perspective.

Table 9 provides a comprehensive overview of potential strategies on a short- to long-term perspective that may be asserted by regulatory agencies directly or as authorized institution.
The overall goal may be to achieve implementation of these strategies globally[73,74], in the EU, USA, Canada and Australia. However, this can only be done in part because the regulatory framework for pharmaceutical approvability, manufacturing, and quality standards is not yet harmonized in all countries world-wide[83].

Table 9 Potential regulatory DS prevention and mitigation strategies

Listed are potential strategies on a short to long -term perspective that may be asserted by regulatory agencies directly or as authorized institution

Prevention and mitigation strategies	
Short- to mid-term	Mid- to long-term
Customized incentive package for manufacturing critical pharmaceuticals[90,93,94]	Global pricing system with minimal price for essential pharmaceuticals[73,74,89]
Create allocation plans[73,90,92]	Financial / economic incentives for MAHs and manufacturers[90]
Development of an early notification system[73,87,89]	Global notification and reporting system[73,74,89]
Development of a mandatory / public reporting system[73,77,87,90,91]	Add DS problem to the life cycle management of a product[73,83]
Development of standardized risk assessment[83,89,90]	Development of appropriate storage and order systems[45,83,87,89,87,90,92]
Development guidance on available alternative treatments[45,54,73,90]	Specialized treatment programs[73]
Regulatory flexibility and enforcement discretion[45,54,83,90]	Reduction and elimination of DS causes[45,47,77,90]
Regulated expediting actions[45,54,90,93]	

One of the main challenges to resolve and thus to end DS is the heterogeneous pricing system for pharmaceuticals world-wide[73]. Initial approaches attempt to define a fair price for pharmaceuticals word-wide, and a complete revision of the pricing procedures including the critical review of tender and procurement practices[83,87,89]. Although regulatory authorities are not supposed to be concerned with pricing, they are constantly drawn into a debate over the cost of pharmaceuticals and reimbursement[97]. Regulatory requirements have made research and development expensive and at the same time public health was improved and economic valued was added. Nevertheless, it cannot be concluded that there is a linear correlation between pharmaceutical prices and their regulatory costs[97].

Four proposals have been made recently on how regulators can contribute to keep pharmaceutical spending sustainable, particularly in the EU. This includes 1) the facilitation of competition due to expedited authorization of generic and 2) me-too products that may drive down pharmaceutical prices, 3) the encouragement of clinical trials that measure value, and 4) the facilitation of collecting and interpreting data important to potential payers[97]. Moreover, EMA tested the *adaptive licensing pathway* in a pilot project that is intended to enable a flexible and staggered approach for clinical development, licensing, and reimbursement by involving relevant decision-makers from regulatory and health technology assessment bodies to jointly agree a data generation plan[100]. Also, in future, the regulatory assessment of the quality, safety, and efficacy of a pharmaceutical will be separated from the pricing and refund decisions to avoid price gouging and decline of high quality medicines standards[97].

IV.A.1. Strategies on a mid- to long-term perspective

a) Global pricing system with minimal price for essential pharmaceuticals[73,74,89]

A globally defined pricing procedure would contribute to achieve transparency of setting a fair minimal price for pharmaceuticals to keep them on the market. This global approach is not easy to achieve and the advantage is still under discussion[73,74,89].

b) Financial / economic incentives for MAHs and manufacturers[90]

The development and marketing of critical pharmaceuticals is unattractive for companies in terms of their economic benefit. To encourage companies to produce critical pharmaceuticals such as orphan and pediatric pharmaceuticals, an incentive program was established including listed patent protection, various forms of statutory market exclusivity, and tax credits.

Based on this, a similar incentive system should be established to attract new entrants to the market by countering the low profit margin that manufacturers associate with producing certain critical pharmaceuticals. In addition, these incentives should help to reorient the industry and to shape the market[73] improving the industrial infrastructure for pharmaceutical production[92]. This requires a long-term cooperation between companies and regulatory authorities.

c) Global notification and reporting system[73,74,89]

A global view on the DS situation by monitoring systems would enhance a joint rapid response to end DS. While an EU-wide standardized notification and reporting system for DS seems possible being a mid-term goal (Chapter IV.A.2), the establishment of a global system requires much more resources and time.

In the US and Canada, the notification of anticipated DS is mandatory, while this is heterogeneous in the EU (Chapter III). Furthermore, the public reporting to various stakeholders is not uniformly regulated. Some companies fear a negative impact with the public reporting of the DS situation. Therefore, a uniform approach for a mandatory public reporting system including a staggered reporting still needs to be discussed with all stakeholders.

d) Add DS problem to the life cycle management of a product[73,83]

Until now, the DS problem is not entirely addressed in the life cycle management of a product.

Already *before approval*, in the developmental strategy a potential DS problem of a pharmaceutical should be addressed, also to sharpen the awareness of industry and regulators regarding DS. Therefore, the risk management plan (EU) or the Risk Evaluation and Mitigation Strategies (US) should outline established strategies to prevent, mitigate and manage potential DS situations. For instance the strategies should be discussed for the case

when only one API supplier is available. In general, at least three different manufacturers are considered desireable[73].
After the approval, when pharmaceuticals are marketed they are prone to DS. Therefore, established strategies need to be revised more often and adapted to actual changes. To give a clear direction, guidance documents such as ICH Q12 describing life cycle management may be revised. Furthermore, GMP inspections by authorities may also focus on reviewing established DS strategies.
When a manufacturer may not be able to produce a new or innovative pharmaceutical e.g. due to technical complications or low profit margin he may consider the withdrawal of the marketing authorization. Therefore, regulatory authorities attempt to establish an anti-withdrawal approach. To avoid pharmaceutical's unavailability, the transfer of the marketing authorization and / or other intellectual properties rights to willing producers should be considered. However, the transfer of the MA is not often used as a solution[83].

These approaches are most important for critical or essential pharmaceuticals. A basic prerequisite is the uniformity of the definition of critical or essential pharmaceutical (Chapter IV.A.2). To make this a global standard, close cooperation between all stakeholders is required.

e) Development of appropriate storage and order systems[45,83,87,89,87,90,92]

In all analyzed countries, a system of security stock unique to each country is available. In principle, this approach is reasonable and should be maintained by regulatory authorities but the costs cannot be ignored and need to be appropriate. Moreover, it is questionable whether a regulated global or uniform system is necessary since requirements are different in each country. For certain, the establishment of fast and traceable allocation plans for critical pharmaceutical is a noteworthy aspect to discuss (Chapter IV.A.2).

f) Specialized treatment programs[73]

In the past, specialized treatment programs, such as vaccines or antiretrovirals were successful in combing single indications. Similar to this, specialized initiatives or programs could be established for indication treated with pharmaceuticals that are most susceptible to DS, e.g. due to high-risk manufacturing because of their complex nature. The establishment of the benefits of such programs requires a long-term cooperation between various stakeholders, in particular patients, physicians, companies and regulatory authorities.

g) Reduction and elimination of DS causes[45,47,77,90]

To end DS situations the underlying causes need to be reduced and eliminated. This requires a deeper understanding of the underlying causes.
Regulatory authorities should support and initiate high level investigations on root causes of DS are necessary. In detail, the risk of shortages, up-to-date inventory information, rate of demand, manufacturing schedules, and order patterns should be assessed and evaluated to

identify best practice approaches and early warning signals of DS. To increase the knowledge, a cooperation of with stakeholder groups should be established. For instance, the FDA for instance publishes an annual report of the progress of DS and the EU has launched a European Medicines Shortages Research Network to investigate DS in more detail.

IV.A.2. Strategies on a short- to mid-term perspective

While regulatory authorities can influence the availability of new pharmaceuticals on the market through approval, they do not possess the legal authority to dictate manufacturers to produce pharmaceuticals[87,90]. This only leads to a limited legal scope of action for regulatory authorities. In the US, FDASIA was enacted to end this situation and also in Canada a similar regulation was introduced coming into effect in 2017 (Chapter I.D). In Europe the EMA needs to be given a clearer legal mandate to be active in this field, e.g. additional legislation would be required to cover decisions made for commercial reasons or to require potential DS to be reported as EMA does not follow DS related to capacity issued or problems in distributions as this is the responsibility of NCA[87]. Legislation generally authorizes regulatory authorities to impose sanctions for those who fail to comply with the requirements; however, penalties seem to run counter and do not resolve problems with DS.

a) Customized incentive package for manufacturing critical pharmaceuticals[90,93,94]

As regulatory penalties do not resolve DS, customized incentive packages provided by regulatory authorities are more favorable. For instance, manufacturers commit to meet certain production and quality levels, and to make manufacturing quality a priority. In exchange the regulatory authorities provide positives incentives, such as tax rebates, waiving of user fee requirements, and expedited approval of new manufacturing processes and facilities.
Moreover, regulatory authorities should promote the public recognition of manufacturers who have demonstrated consistent records of high quality manufacturing and effective risk remediation plans. In particular, regulatory incentives should encourage manufacturers to decouple quality considerations from purchasing decisions that intensify pricing competitions. This should support the effort by buyers to buy only from manufacturer with a history of good quality, include “failure to supply” clauses in purchasing contracts. In addition, incentives could imply a reduced oversight of manufactures by regulatory authorities who maintain good compliance histories. For instance, a reduced oversight could include the downgrading of filing categories for site transfer and up-scaling of manufacturing capacity. Furthermore, granting additional exclusivity for products in the same therapeutic areas as the pharmaceutical in shortage to manufacturers who consistently maintain high quality manufacturing standards could be considered
These approaches are ranked to be activities for a mid-term perspective. The FDA already started assigning positives incentives for manufacturers, and also benefits through a *qualified manufacturing partner program* are available. These approaches may be modified and used by other regulatory authorities.

Notably, the underlying scoring system to evaluate the manufacturing quality metrics needs to be examined further, e.g. the calculation of the most favorable facility design, supply chain analytics using *big-data*, and the investigation of economic principles to forecast inventory requirements might be important.
Again, this is a multi-stakeholder approach and needs collaborative action.

b) Create allocation plans[73,90,92]

Allocation plans are of great interest because as is important to prioritize the use of pharmaceuticals in short supply. This affects not only the delivery to countries in need but also the supply of vulnerable patient groups, such as children or elderly. Therefore, supply chain management systems are required to be installed and improved. Regulatory authorities should request and support the development of specialized and appropriate IT systems, such as the use of the *GS1 bar code system* to identify, capture and share supply chain information[101].

c) Development of an early notification system[73,87,89]

All stakeholders acknowledge that an early notification system is indispensable to take appropriate actions to resolve upcoming DS. In most high-income countries a notification system is established but most of the low-income countries still do not have one.
For the EU, a central contact point was suggested to address DS aiming at a joint rapid response[87]. However, this requires resources that maintain, validate and verify the sources. Most importantly, regulatory authorities should primarily focus on the development of common definitions aiming at comparable data sets and a best practice approach for regulatory authorities. Also regulatory authorities need to be given a clearer legal mandate to require early notification of potential DS.
For a long-term perspective, a common notification platform could be established.

d) Development of a mandatory / public reporting system[73,77,87,90,91]

While it is easier to achieve a mandatory notification process, the mandatory reporting of DS is much more challenging.
In the US and Canada, the reporting of DS situation on the website is mandatory; this is not the case in Australia, however, the TGA is authorized to report DS even without sponsor's consent. In the EU, mandatory reporting is not legally binding and very uniformly regulated (Chapter III).
Companies, especially those with business strategies focused on pharmaceuticals that are most susceptible to DS due to their complex manufacturing, fear that the perennial publishing of their name will have a negative impact on their businesses. Therefore, they used to refuse to report DS. To stop this loop and to enhance communication of all stakeholders the development of a staggered approach seems to be favorable. For instance, reporting a DS depends on pharmaceutical and the outcome of a proper, standardized risk-assessment not to overload stakeholders with information[91]. Furthermore, a standardized way of presenting DS information, such as on websites should be established.

e) Development of standardized risk assessment[83,89,90]

A lot of actions to take during DS depend on a risk assessment of the pharmaceutical in shortage. Usually the manufacturer conducts a risk assessment to evaluate if the DS needs to be reported to the regulatory authority. Then, the regulatory authority conducts a risk assessment of the pharmaceutical in shortage to evaluate if there is a need to report this DS further to other stakeholder. In all analyzed countries, not only the requirements to notify and report DS are different, also the risk assessment of pharmaceuticals in shortage is different. Therefore, there is a high need in harmonizing the risk assessment approach.
In 2014, the Parenteral Drug Association published a template for a *risk triage approach* to proactively manage DS[101]. This template consists of three steps: 1) an assessment of the impact on patients including an assessment of alternative therapies, 2) an assessment of the likelihood of the DS to define the priority, and 3) the triage output regarding the prevention and response plan.
Regulatory authorities should aim at implementing similar approaches to assess the risk of the pharmaceutical in shortage to determine further actions.

f) Development of an essential medicines list[83,89,90,91]

Depending on the nature of the pharmaceutical and the complexity of the manufacturing process some pharmaceuticals are more susceptible to be in shortage. A promising approach is the development of an essential medicines list, which should contain pharmaceuticals that are highly susceptible of DS or pharmaceuticals for certain indications or patient groups. This might facilitate a rapid response when a DS situation develops; however, the content and the procedure to add pharmaceuticals to this list have to be discussed in more detail.

g) Development guidance on available alternative treatments[45,54,73,90]

In connection to a standardized risk assessment, also guidance should be made available to HCP, pharmacists, and patients to identify available treatment alternatives when a DS occurs. Ideally, a central contact point is available for that purpose. For instance, in Canada the *drug product database* can be used to find alternative medications and in the US, comprehensive information on therapeutic equivalence can be found in the *orange book*.
Furthermore, the development of a *best practice* approach for regulators and all stakeholders should be considered to make specific, tailored treatment recommendations[89,73].

h) Regulatory flexibility and enforcement discretion[45,54,83,90]

It was found that in case of a DS due to manufacturing issues, 57.9% of the manufacturers for sterile pharmaceuticals (38.1% of non-sterile pharmaceuticals) appreciated quick approvals of new production lines to increase the manufacturing capacity, and 36.8% vs. 19% of the manufacturers appreciated input by regulatory authorities on their investigations. Moreover, requests by regulatory authorities for other companies to increase their production and searching overseas for pharmaceuticals helping to make up supply deficiency was acknowledged by manufacturers[75].

This survey showed that DS are specific situations that require tailored response by regulatory authorities. These may include temporary exercises of regulatory flexibility and enforcement discretion to facilitate e.g. new sources of medically necessary pharmaceuticals or special lot and batch release actions, GMP inspections, MA exceptions and repackaging. Moreover, import of pharmaceuticals from other markets might be enabled or export of necessary pharmaceuticals might be controlled.

i) Regulated expediting actions[45,54,90,93]

In addition to the unplanned actions of regulatory flexibility and enforcement discretion described above, also regulated expediting actions should be available in case of DS.
Submissions from manufacturers attempting to up-scale, improve or restore the production should be offered the possibility of expediting the review of variations or inspections. Moreover, an expected approval of specific lots or batches of critical pharmaceuticals should be facilitated.

IV.B. Prospective challenges

The continued access to high-quality, effective, and safe pharmaceuticals is one of the priorities of regulatory authorities. Another regulatory priority is assuring the availability of new and innovative pharmaceuticals.

The global problem of DS is known since decades and numerous approaches and strategies have been developed in the past to prevent, mitigate, and manage DS situations (Chapter IV.A). However, a global strategy to this complex phenomenon has not been found yet. In addition, new trends and challenges are emerging that also might influence DS strategies in the near future. In particular, the role of regulatory authorities has to be revised and strengthened accordingly. Regulators should be involved more closely in the development of innovative pharmaceuticals to avoid losing track of new trends of innovative pharmaceuticals.

Precision or personalized medicines represent a new era and trend of innovative pharmaceuticals[99].
Precision Medicine takes into account individual characteristics of each patient and consequentially, an individual medical treatment is tailored to this patient achieving higher treatment benefits[103]. It has to be examined whether the approach of precision medicines will possess a higher risk to DS e.g. due to their small group of benefiting patients.

In addition, novel technologies, such as a 3D printer, are already available to support in resolving DS[98]. Researchers have developed a system the size of a refrigerator that can synthesize a multiple pharmaceuticals from start to finish in short periods of time meeting the US standards, including an antihistamine, an antidepressant, a local anesthetic, and a central nervous system depressant[98]. This system could be used to create active ingredients on

demand, helping to prevent DS and to respond quicker to disease outbreaks. In addition, it may be an alternative for synthesizing pharmaceuticals for only a small group of patients[98].

IV.C. Summary

DS are a globally realized phenomenon since decades. The causes and relations underlying DS are various and not easy to understand. All stakeholders in the healthcare system are tremendously impacted when a DS occurs; therefore resolution to end DS is urged.

Potential regulatory actions that can be implemented on a short to long-term perspective to prevent and mitigate DS have been described. For most of the prevention and mitigation strategies, interdependencies to each other were seen.
Potential strategies that can be implemented on a mid- to long term perspective comprise a global pricing system, financial and economic incentives for the pharmaceutical industry, a global notification and reporting system, and the development of appropriate storage and order systems. Furthermore, DS should be included in the life cycle management of pharmaceuticals and most important, the causes of DS need to be reduced and eliminated.
Potential strategies that can be introduced on a short- to mid-term perspective include the development of an essential pharmaceuticals list and a standardized risk assessment, guidance on available treatment alternatives and an early notification and reporting system per country. Moreover, expediting actions and temporary exercises of regulatory flexibility and enforcement discretion by authorities will help to reduce DS situations.
A summary of the most important interdependencies of potential strategies is shown in Figure 13.

The intensity of regulatory governance in DS situations is limited due to lacking legal power of authorities. In addition to implemented DS reporting systems, no further novel measurements were introduced but improved integration and utilization of already existing measures, e.g. expediting reviews was focused and extended.

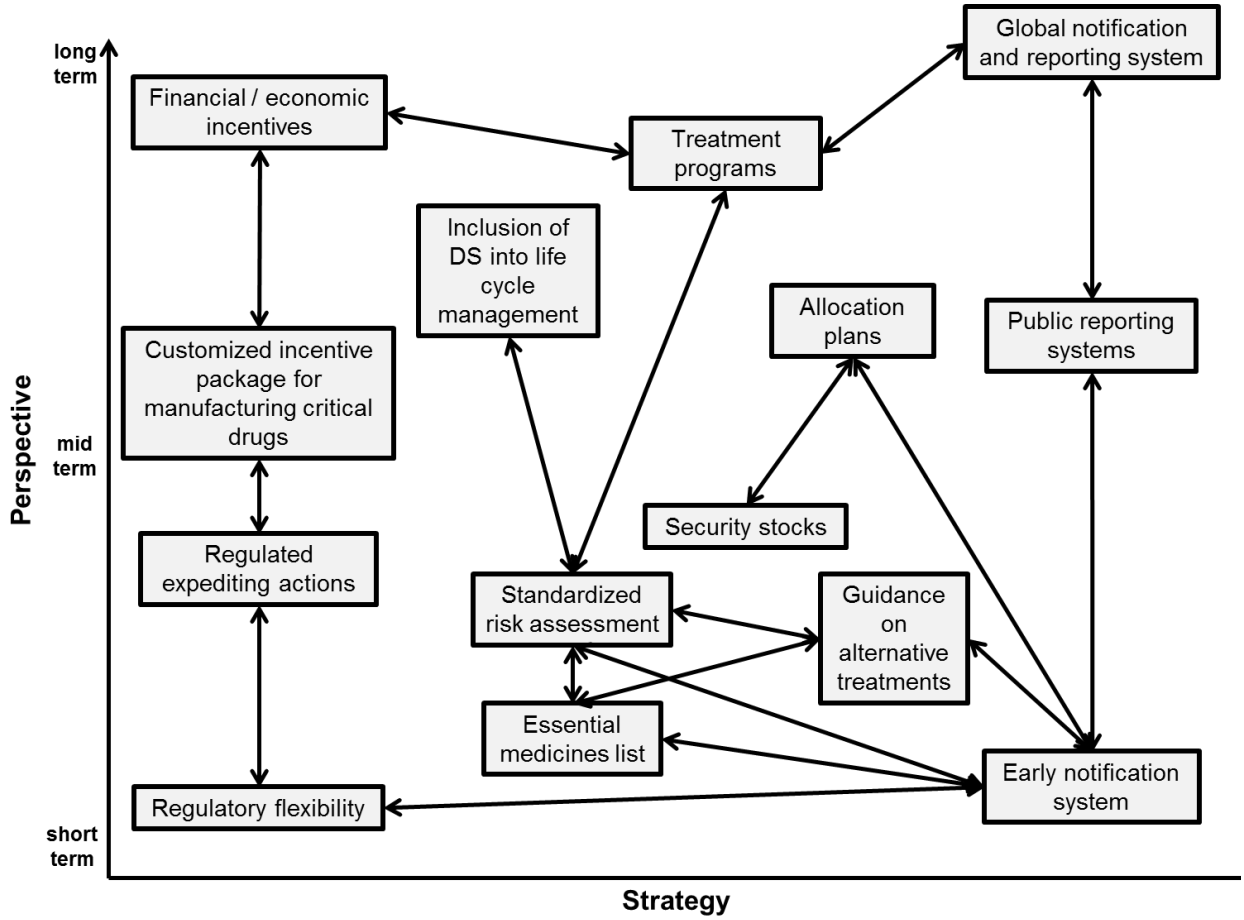


Figure 13 Interdependencies of DS prevention and mitigation strategies

Shown are potential temporary interdependencies of the implementation of DS prevention and mitigation strategies. For more details see text.

V. OUTLOOK AND SUMMARY

DS are a complex and global phenomenon currently on the rise. Every stakeholder in the health care system is affected as soon as a pharmaceutical cannot be delivered to a patient in need.

This work laid out an overview of the landscape of pharmaceutical shortages in the EU, the US, Canada, and Australia, and provided insights into regulatory coping strategies.
First, legal provisions regarding DS were examined in the four industry nations. It was shown that the legislation in the EU contains provisions about the responsibilities of NCAs and MAHs, but no further details regulating DS. In the USA and Canada detailed legal guidance on DS is available, whereas in Australia a voluntary procedure under control of the TGA is available.

Furthermore, the availability of information on DS published on websites of agencies was examined showing that the available information is very varied. The organization of websites of EMA, FDA, Health Canada and TGA appear to be globally aligned, whereas websites of European NCA are more diverse.
A scoring system was developed to evaluate the granularity of published DS information. The majority of analyzed reporting websites showed low to medium granularity, while only a few showed high granularity. Interestingly, the leading regulatory agencies EMA, FDA, Health Canada and TGA were found to be as heterogeneous as the NCA in the EU. Four different types of DS reporting systems on the websites were found: 1) a searchable database, 2) shortage list on their website, 3) table in PDF or Excel format, and 4) DS information within other reports. The scored evaluation indicated that a well-structured and organized DS reporting system is important for the users to easily and rapidly find that information they need. However, a direct practical benefit of transparent reporting websites still needs to be demonstrated.

In the EU, DS were found to be within the responsibility of each member state but an EU-wide Incident Management Plan was implemented to cope with DS that affect more than one MS. In the US, the provisions of FDASIA changed the landscape of DS management by handing over more legal power to the FDA. At FDA the Drug Shortage Staff was established to secure appropriate DS management including rapid notification, reporting, and communication.
In spring 2017, provisions will come into effect in Canada that tightly regulates a multi-stakeholder approach in managing DS situations. In Australia, only a multi-stakeholder guidance for DS is available. Essentially, there is no common approach of managing DS situation in all countries, but yet the three pillars notification as early as possible, structured assessment, and coordinated responses seem to be the most crucial factors.
Up to now, no reliable data is available showing the benefit of different DS management approaches. In general, it was found that once a DS situation occurs, the management is

faster and easier when a structured and coordinated process comes into effect. Whether this process needs to be initiated by a higher regulatory body or provisions are required to regulate these processes need to be investigated further.
Moreover, regulatory prevention and mitigation strategies were examined. It was found that administrative, legislative, and industry approaches to address DS have focused on the symptoms rather than the causes. Regulatory authorities are constrained in their actions due to limited of legal power. Besides the implementation of a DS notification and reporting system, no further novel regulatory measurements were implemented. Instead, already existing measures, e.g. expediting reviews, were focused and extended. Potential regulatory actions can be implemented on a short- to long-term perspective and were found to be highly interdependent to each other. These potential strategies comprise a global pricing system and financial and economic incentives for the pharmaceutical industry, and the development of an essential pharmaceuticals list and a standardized risk assessment including guidance on available treatment alternatives, respectively.

The overall aim in preventing and mitigating DS is to eliminate the underlying causes. However, this is challenging and a global, multi-stakeholder task. To what extent new, and innovative medicine trends, (e.g. precision medicines), possess an increased risk for DS situations needs to be investigated in more detail. Interestingly, also novel technologies, such as a 3D printer, are already available to produce pharmaceuticals on demand and thus resolve DS.

ANNEX I

Table 10 Websites scanned for information on DS, alphabetically arranged

See Table 4 (EU) and

Table 5 (selected countries) in the text, and Figure 3 for a summary.

Country	Institution	Website with information on DS	Remarks	Accessed
Australia	TGA	https://www.tga.gov.au/medicine-shortages-information-initiative Search medicines shortage: http://apps.tga.gov.au/prod/MSI/search/	n / a	Aug 21, 2016
Austria	AGES; BSAG	http://www.basg.gv.at/news-center/news/news-detail/article/uebersichtsliste-vertriebseinschraenkungen-986/ Current list of pharmaceuticals in shortage due to interrupted supply available as pdf	No information available on AGES website, BASG seems to be responsible	Aug 21, 2016
Belgium	FAMHP	http://www.fagg-afmps.be/nl/news/news_indisponibilite_plateforme List of unavailable pharmaceuticals: http://www.fagg-afmps.be/nl/items-HOME/Onbeschikbaarheid_van_geneesmiddelen	Language of search: Dutch#	Jul 17, 2016
Bulgaria	BDA	http://www.bda.bg/ No information available	Language of search: English and Bulgarian#	Jul 17, 2016
Canada	Health Canada	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/shortages-penuries/index-eng.php reference to website http://www.drugshortages.ca/drugshortagehome.asp, and Drug Shortages Records: http://www.drugshortages.ca/drugshortages.asp http://www.canadadrugshortage.com/	Drug Shortages Records is not maintained by Health Canada	Aug 21, 2016
Croatia	HALMED	http://www.halmed.hr/en/Promet-proizvodnja-i-inspekcija/Promet/Prekid-opskrbe-trzista-lijekom-i-nestasice/ List - Discontinuation of drug supply (Prekid opskrbe tržišta lijekom) and Shortage of medicines (Nestašice lijekova)under “download”	Language of search: English# Lists published on website in Croatian;	Aug 21, 2016
Cyprus	MOH	http://www.moh.gov.cy/moh/moh.nsf/index_gr/index_gr?OpenDocument Very limited information in Greek available, no information available in English, a lot of the subpages are not translated	Language of search: English and Greek#	Jul 17, 2016
Czech	SUKL	Medicinal Product Database including shortages:	n / a	Jul 17,

Republic		http://www.sukl.eu/modules/marketreport/search.php?data%5BNAME%5D=&data%5BCODE%5D=&data%5Breport_type%5D=&data%5Breport_reimb%5D=&data%5Breport_from%5D=&data%5Breport_to%5D=&data%5Bdate_from%5D=01%2F01%2F2016&data%5Bdate_to%5D=01%2F07%2F2016&x=49&y=13		2016
Denmark	DKMA	Information on reporting serious supply difficulties:http://laegemiddelstyrelsen.dk/en/licensing/supervision-and-inspection/serious-supply-difficulties No information available on drug shortages, no database or shortage list	Search function lacking	Jul 17, 2016
Estonia	RAVIMIAMET	http://www.ravimiamet.ee/en No information available	Language of search: English and Estonian#	Jul 17, 2016
EU	EMA	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000588.jsp&mid=WC0b01ac05807477a5 Shortage catalogue: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000376.jsp&mid=WC0b01ac05807477a6	n / a	Aug 19, 2016
Finland	FIMEA	Shortage list: http://www.fimea.fi/tietoa_fimeasta/ajankohtaista/saatavuushairiotiedotteet Only available in Finish	Language of search: English and Finish#	Jul 17, 2016
France	ANSM	http://ansm.sante.fr/S-informer/Informations-de-securite-Ruptures-de-stock-des-medicaments Only available in French	Language of search: French#	Jul 17, 2016
Germany	BfArM PEI	http://www.bfarm.de/DE/Arzneimittel/zul/amInformationen/Lieferengpaesse/_node.html http://www.pei.de/DE/arzneimittel/impfstoff-impfstoffe-fuer-den-menschen/lieferengpaesse/informationen-lieferengpaesse-impfstoffe-node.html	Language of search: German and English	Jul 17, 2016
Greece	EOF	http://www.eof.gr/web/guest/shortage For further information log-in data are required	Language of search: Greek	Jul 17, 2016
Hungary	OGYEI	https://www.ogyei.gov.hu/_atmeneti-termekhiany_/ Only available in Hungarian	n / a	Jul 17, 2016
Iceland	IMCA	http://www.ima.is/ No information available	Language of search: English and Islandic#	Jul 18, 2016
Ireland	HPRA	Shortage information can only be found within the safety notices: https://www.hpra.ie/homepage/site-tools/search?query=shortage	n / a	Jul 18, 2016

Italia	AIFA	http://www.agenziafarmaco.gov.it/it/content/carenze-dei-medicinali List of current DS: http://www.agenziafarmaco.gov.it/sites/default/files/elenco_medicinali_carenti_11.07.2016.pdf Only available in Italian	Language of search: English and Italian[#]	Jul 18, 2016
Latvia	SAM	https://www.zva.gov.lv/index.php?id=4&rel=2771 List of shortages: https://www.zva.gov.lv/?id=781&top=334&sa=673	n / a	Jul 18, 2016
Liechtenstein	Office of Health	http://www.llv.li/ No information available	n / a	Jul 18, 2016
Lithuania	VVKT	http://www.vvkt.lt/ No information available	Language of search: English and Latvian[#]	Jul 18, 2016
Luxembourg	Ministry of Health	http://www.sante.public.lu/fr/politique-sante/ministere-sante/index.html No information available, reference to Belgium	Language of search: French[#]	Jul 18, 2016
Malta	Medicines Authority	Medicines database available, but no information on DS http://medicinesauthority.gov.mt/medicinesdatabase	n / a	Jul 18, 2016
Netherlands	IGZ	http://english.cbg-meb.nl/human/for-marketing-authorisation-holders/contents/post-marketing-authorisation/possible-shortages-of-medicinal-products Shortage Database: https://farmanco.knmp.nl/ (only available in Dutch)	Language of search: English and Dutch[#]	Jul 18, 2016
Norway	Medicines Agency	Medicines database available, but no information on DS http://www.legemiddelverket.no/English/Database_approved_and_marketed_pharmaceuticals/Sider/default.aspx	Language of search: English and Norwegian[#]	Jul 18, 2016
Poland	URPL; GIF	http://www.urpl.gov.pl/pl https://www.gif.gov.pl/ No information available[$]	Language of search: English and Polish[#]	Jul 18, 2016
Portugal	INFARMED	Database available, requires log-in data, only available in Portuguese https://gam.infarmed.pt/Login.aspx	Language of search: English and Portuguese[#]	Jul 18, 2016
Romania	ANM	Information on DS amongst *important notification* http://www.anm.ro/anmdm/en/med.html	n / a	Jul 18, 2016
Slovakia	SUKL	Medicinal Product Database, but no information on DS: http://www.sukl.sk/en/servis/search/searching-on-the-database-of-medicinal-products?page_id=410	n / a	Jul 18, 2016
Slovenia	JAZMP	List of indispensable pharmaceuticals, but no information on DS available	n / a	Jul 18,

		http://www.jazmp.si/en/human_medicines/indispensable_medicinal_products/		2016
Spain	AEMPS	http://www.agemed.es/medicamentosUsoHumano/problemasSuministro/home.htm Database with information on DS: http://www.aemps.gob.es/cima/fichasTecnicas.do?metodo=detalleForm List of pharmaceuticals in shortage: https://cima.aemps.es/cima/fichasTecnicas.do?metodo=buscarDesabastecidosResueltos Only available in Spanish	Language of search: English and Spanish#	Jul 18, 2016
Sweden	Medical Products Agency	National register of medicinal products per log-in, content not known: https://npl.mpa.se/mpa.npl.services/home2.aspx	Language of search: English and Swedish#	Jul 18, 2016
United Kingdom	MHRA	www.mhra.gov.uk - No information available§ Pharmaceutical Services Negotiating Committee publishes information: http://psnc.org.uk/dispensing-supply/supply-chain/branded-shortages/	n / a	Jul 18, 2016
USA	FDA	http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ Drug Shortage Database: http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm	n / a	Aug 21, 2016

When information was not available in English, the national language was used for evaluation. Web-based translators were utilized supportively (http://dict.leo.org/ende/index_de.html; https://translate.google.de/)

$ Privately funded website available (http://www.leki-informacje.pl/urpl)

§ Website of Pharmaceutical Services Negotiating Committee contains information (http://psnc.org.uk/dispensing-supply/supply-chain/branded-shortages/ / http://psnc.org.uk/dispensing-supply/supply-chain/generic-shortages/)

ANNEX II

Table 11 Evaluation matrix, degree / level of available information

See Table 6 (EU) and Table 7 (selected countries) in text.
For each information a score of one point was awarded. Only websites were examined where information has been available, others were excluded from survey.

Published Criteria	AT# AGES	BE# FAMHP	HR# HALMED	CZ SUKL	FI FIMEA	FR# ANSM	DE# BfArM PEI	HU# OGYEI	IEF HPRA	IT# AIFA	LV# SAM	NL# FARMANCO	RO ANM	ES# AEMPS	EU EMA	US FDA	CA* Health Canada	AU TGA
Brand Name	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X	X
INN	X	-	X	X	X	X	X	X	X	X	X	X	-	X	X	X	X	X
MAH	X	X	X	X	X	X	X	X	X	X	-	X	-	X	-	X	X	X
National Authorization Number	-	X	-	X	X	X[E]	X	-	(X)	X	X	-	-	X	-	X	X	X
ATC code	-	-	-	X	X	-	-	X	(X)	-	-	-	-	X	-	-	-	-
ATC name	-	-	-	X	-	-	-	-	-	-	-	-	-	X	-	-	-	-
Indication	-	-	-	-	X	X	-			-	-	-	-	-	X		-	-
Reason for DS	X	X	X	X[B]	X	X	X	X	(X)	X	-	X	X	X	X	X[H]	X	X
Overview current Shortages	X	X	X	X	X	X[E]	X	X[E]	X	X	X	-	X	-	X	X	X	X
Overview resolved Shortages	X	-	-	X	-	-	-	-	-	-	-	-	X	-	X	X	-	X
Anticipated Shortages	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Discontinued MP	-	-	X[I]	X	-	X	-	X	-	X	X[I]	X	X[I]	X[I]	X[I]	X	X	X
Proposed date of resolution	X	X	X	X	X	X[E]	X	X	(X)	X	X	X	(X)	X	-	X	X	X
Actual date of resolution	X	-	-	X	-	-	-	-	-	X	-	X	-	X	-	X	-	X
First published	X	X	X	X	X	X	X	-	X	X	X		X	-	X	X	X	X
Last updated	-	X	X	X	X	-	X	X	-	X	X		-	X	X	X	X	X
Pharmaceutical form[C]	-	X	-	X	X	X	-	-	(X)	X	-	X[G]	X	X	-	-	X	X
Packaging	-	X	X	X	-	-	X[E]	-	(X)	-	-	-	-	-	-	-	X	X
Packaging Size	X	X	X	X	X	X	X[E]	X	(X)	-	X	-	-	X	-	-	X	X
Strength[C]	-	-	-	X	-	-	-	-	(X)	X	X	X[G]	-	-	-	-	X	X
Information to HCP	X	-	-	-	X	X[E]	X	-	X	-	-		-	-	X	X	-	-
Information to patients	-	-	-	-	-	-	-	-	-	-	-		-	-	X	-	-	X

Information letter from MAH	-	-	-	-	-	X	-	-	X	-	-		-	-	-	-	-	-
Information on alternate medicines or supplements	-	-	-	X	X	X[E]	X[E]	X	(X)	X	X	X	X	-	-	-	-	-
Further recommendation	-	-	-	-	X	X[E]	-	-	(X)	-	-	X	-	-	-	-	-	-
Special remarks	-	-	-	X		X[D]	X	-	-	X	-	X	-	-	-	-	-	X
Mandatory storage – essential MP	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Import information	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-
Search for therapeutic categories	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-
Information on stock(s)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-
UPC/GTIN[J]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
searchable/search engine	-	-	-	X	-	X	-	-	-	-	-	X	-	X	-	X	X	X
Overall Score	**11**	**11**	**11**	**20**	**15**	**16**	**14**	**11**	**7**	**15**	**11**	**14**	**8**	**13**	**11**	**14**	**15**	**20**
Published Criteria	**AT#**	**BE#**	**HR#**	**CZ**	**FI**	**FR#**	**DE#**	**HU#**	**IEF**	**IT#**	**LV#**	**NL#**	**RO**	**ES#**	**EU**	**US**	**CA***	**AU**
	AGES	FAMHP	HALMED	SUKL	FIMEA	ANSM	BfArM PEI	OGYEI	HPRA	AIFA	SAM	FARMANCO	ANM	AEMPS	EMA	FDA	Health Canada	TGA

***** Legally binding website not yet available; data from voluntary website was included

[#] When information was not available in English, the national language was used for evaluation. Web-based translators were utilized supportively (http://dict.leo.org/ende/index_de.html; https://translate.google.de/)

[B] Type of announcement is published as default criterion, but no actual reason is explained

[C] Information can be found as due to being part of brand name or generic name; however, here it represents a separate criterion

[D] Lots of information are published here also containing information belonging to the other criteria (relevant information cannot be found quickly)

[E] Information is available but not as separate criterion

[F] No list of Shortages publishes on website of NCA. Information originates from HCP letter written by MAH, and published by NCA. Letters do not follow standard specification, therefore information were set in brackets

[G] Summarized in category "product description" (NL: "Productomschrijving")

[H] as defined per FDASIA, see also Chapter I.D

[I] Information available, but on a different website

[J] GTIN - Global Trade Item Number; UPC – Universal Product Code

Brackets indicate that the respective information can be found on the website on a case by case basis, not all entries follow a standardized format

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EIDESSTATTLICHE ERKLÄRUNG

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Datum Unterschrift

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