Managing Pharmaceutical Shortages:

An Overview and Classification of Policy Responses in Europe and the USA

Abstract

This exploratory paper gives a cross-sectional account of how established health care systems have responded to the novel challenge of drug shortages (DS). In line with previous research, our analysis confirms the existence of strong path dependence in the adoption of policy responses. This path dependence is manifested in a pronounced typology of response patterns where jurisdictional approaches to DS management differ along two core dimensions. These are the salience attributed to the problem, and the level to which state organisations engage with the problem. These patterns are mirrored in the conceptual framing and strategic orientation of the respective DS policies, with Spanish and Irish DS policies focusing on the individual product level and being largely reactive; US policies focusing on the therapeutic level with a focus on mitigation; and German and Austrian policies seeking to address the active ingredient level with a proactive focus on shortage prevention. Despite the importance of legacies, we find evidence of innovation and path creation particularly in relation to the US and German approaches, which we explain by the simultaneous occurrence of internal crisis with pressures from local stakeholders.

Keywords:

Drug shortages, path dependence, policy innovation, strong state, weak state, network governance

Introduction

The past four decades have seen wide-ranging reforms of the health care systems (hereafter HCS) of industrialised nations. Simonet (2011, p.823) notes that this has entailed a pervasive increase in cost awareness with "rising insurer competition in Germany, the separation of care delivery and financing in the UK, health care networks in France and regional delegation in Italy all signalling a will to manage healthcare expenditure more efficiently". This cost

awareness is known to encompass virtually all aspects of healthcare including service and goods components in the broadest sense (Simonet, 2017).

Up until about 2009, pharmaceuticals spending by HCS had largely been seen within this cost-centred lens, with authors such as Vuorenkoski, Toiviainen & Hemminki (2008) documenting the prioritisation of pharmaceutical expenditure control in various HCS. More recently, the increased extent and severity of global pharmaceutical shortages has added a new, unwelcome dimension to the management of medicines within HCS (Fox, Sweet & Jensen, 2014). There is now an ever-looming threat of frequently occurring pharmaceuticals shortages which affects which affects virtually all HCS.

Pharmaceutical shortages present a qualitatively new phenomenon that differs in fundamental ways from classical cost saving and pharmaceutical rationing. Pharmaceutical rationing is linked to ostensibly rational cost-containment decisions, arising when foreseeable limitations on financial resources necessitate the full or partial withholding of a potentially beneficial drug from patients on grounds of affordability (Williams, Robinson & Dickinson, 2012). While there is no reliable estimate as to the prevalence of this type of rationing, there is evidence of HCS making efforts to limit access to expensive new drugs (see, e.g., Gornall, Hoey & Ozieranski, 2016). This is perhaps not surprising given that for 2015 pharmaceutical spending comprised between 12% and 18% of total national health care expenditure in OECD countries (OECD, 2018).

By contrast to classical rationing decisions, which are usually based on detailed cost-benefit data, the challenge of pharmaceutical shortages relates to the unexpected unavailability of a drug, often without precise knowledge of when, or if, the desired drug will be available again, what alternatives are available, and/or which risks the use of these alternatives entails. As such, drug shortages (hereafter DS) present unfamiliar territory to HCS, which usually have little or no experience in managing uncertainty as regards the availability of drug supplies. In other words, while reforms may have prepared HCS to cope with constraints in financial resources, there is little or no experience, or precedent, in terms of managing uncertainties in key supplies.

The purpose of this paper is to identify the primary policy trajectories and approaches a mix of jurisdictions have adopted to cope with the DS crisis. In investigating this issue our approach is both data driven and selective. The jurisdictions chosen for analysis [European Union as represented by the European Medicines Agency (EMA), the US, Germany, Spain, Austria, and Ireland] include entities for which there is both accessible information in relation to the incidence of pharmaceutical shortages, and documentation that allows for an analysis of key policies adopted in response to this problem. Additionally, our analysis suggests that these jurisdictions represent demonstrably different response patterns. The paper gives a cross-sectional account of how established HCS have responded to this emerging challenge, and examines the degree to which these responses mirror historical policy trajectories, or alternatively, have led to the adoption of novel approaches.

Pharmaceutical Shortages as Global Problem

Pharmaceutical shortages have come to present an increasing problem to HCS since the mid to late 2000s (Fox & Tyler, 2009). The problem has been recognised by the World Health Organisation (WHO) from about 2009 onwards (Fox et al., 2014). Active measures to address this issue were taken by the WHO from 2015 onwards when the organisation called a consultation meeting on global pharmaceutical shortages (WHO, 2016). Resultant WHO reports noted that medicines shortages were increasing, particularly for older, off-patent drugs and treatments that are difficult to formulate. DS also included many commonly used medicines such as antibiotics, cancer and cardiovascular medicines, and anaesthetics (WHO, 2016, p. 180). The WHO summarised the primary causes of shortages as: difficulties in acquiring raw materials; manufacturing problems; competition issues; business decisions; impact of new technology; expensive medicines; and market fragmentation (WHO, 2016, p. 181).

This paper focuses on approaches to the management of pharmaceutical shortages as they have emerged within developed countries' HCS. This focus on developed country HCS relates to the observation made by the WHO that such approaches have not developed significantly elsewhere because "unreliable data from peripheral facilities continue to be a major problem in most low- and middle income countries, hindering coordinated stock management and effective forecasting" (WHO, 2016, p. 2). The discussion here centres on the US and Europe where responses have evolved and data and policy documents in relation to shortage management are available.

Our paper is structured in three parts. Part one discusses definitions of pharmaceutical shortages and summarises the literature on their causes. Part two describes policy measures across a number of jurisdictions with a focus on shortage lists as they are currently collated and disseminated. Part three categorises existing approaches with a view toward identifying continuities and novelty in this emerging area of policy making.

Defining pharmaceutical shortages

De Weerdt, Simoens, Casteels and Huys (2015) highlight how definitions of a DS differ at organisational levels. They suggest that the objectives of the institution constructing a definition will mirror their own perception as to whether shortages are a technical supply-chain issue; or one based on market issues, such as pricing, level of competition, and/or the policies of funding agencies. They find twenty different definitions, with variances arising from "when does a supply problem become a shortage, permanent and/or temporary shortages, the typology and time frame of DS" as well as differences resulting from the fact that some regulatory agencies focus on clinically essential drugs and/or limit the definition of shortages to those drugs for which there is no alternative (De Weerdt et al., 2015, p. 1). Despite this variety of definitions (WHO 2017), De Weerdt et al. (2015) observe that many of these classifications are not comprehensive, in that some do not include permanent discontinuations of drugs. Bogaert, Bochenek, Prokop and Pilc (2015, p. 2) suggest that differing national timelines for identifying shortages, and different national emphases on the locus of a shortage can make cross-national comparisons difficult. Even where definitional approaches are seemingly uncomplicated or apolitical, they can sometimes reflect complex assumptions about institutional capacities of key components of HCS, such as those of prescribers.

A key source of complexity in this matter is the degree of granularity with which a shortage is considered. Product, and especially detailed branded product-based definitions and indicators of shortages, can be unhelpful, if the focus is on ensuring and managing an adequate supply of therapeutic options, as one would expect it to be from a public health perspective. Here a whole other range of considerations may come into play before the absence of a specific product represents genuine DS from a HCS perspective. These include the availability of therapeutic alternatives which provide the same or similar benefits without posing significant risks to patients (Ventola, 2011).

The original US Food and Drug Administration (FDA) definition of DS reflected such an ambitious approach. Here DS were described as "a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the patient level" (FDA, 2011, p. 1). This definition had the potential for establishing relatively narrow parameters for the definition of shortages in that it identified shortages as situations where there were no other clinical options to the drug that was unavailable (Ventola, 2011). The FDA has now adopted a more basic definition of DS which defines these as "a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug" (FDA, 2017, p. 14).

Both past and present US FDA approaches differ from the somewhat narrower focus taken by the EMA. The EMA (2013a, p. 1) provides an implicit definition of DS as part of its shortages list (launched in 2013), by stating that this includes "medicine shortages that affect or are likely to affect more than one European Union (EU) Member State, where the EMA has assessed the shortage and provided recommendations to patients and healthcare professionals across the EU." This is coupled with the statement that the organization "does not give a complete overview of all medicine shortages occurring in the EU, as most shortages are dealt with at a national level" (EMA, 2013a, p. 1). Accordingly, it is not medical necessity alone, but multi-jurisdictional unavailability that is required for a shortage to be identified. Further complexity arises in monitoring quality and DS because EU requirements to list manufacturers on drug labels are not mirrored in the US (Woodcock and Wosinska 2013).

A widely recognised problem in assessing the extent of pharmaceutical supply deficiencies is that it is difficult to distinguish between specific stock keeping unit shortfalls, arising, for instance, from a specific dosage unit being unavailable while the drug itself is accessible in other forms/doses, as opposed to more insurmountable or genuine DS at the level of active ingredient. In response to this, professional organisations such as the American Society of Health-System Pharmacists (ASHP) have suggested that the focus of attention should be on upstream impact with a DS being understood as "supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent" (ASHP, 2009, p. 1399). This approach, if fully developed, would classify DS according to the potential harm they could cause and/or the resources and efforts it would take to manage and ameliorate them. The ASHP's own DS list accordingly provides information on: a) the

specific product affected by dosage and trade name, b) reasons for the shortage, c) estimated resupply dates, and d) related shortages.

From a regulatory or health policy standpoint, this type of information can present valuable input into DS management processes process in which, very short-term, replaceable/manageable or non-essential shortages, and hence relatively harmless DS, are clearly distinguished from others; and the attention of regulators and policy makers is then paid to chronic, recurring and dangerous shortages of significant public and health policy relevance. We discuss the extent to which such an approach has been adopted in different jurisdictions later in this paper. Additionally, the current ASHP list, with its identification of specific underlying causes of a shortage, allows for broader policy interventions which could involve multi-stakeholder high-level discussions in line with the current German 'pharmaceutical shortages' jour fixe where senior representatives from government, industry and medical and pharmaceutical services providers meet to discuss how to address existing or projected shortages (BfArM, 2016). While in the US communication between the FDA and pharmaceutical suppliers and producers has increased, there is little evidence that the organisation is posed to follow a similar model (Schweitzer, 2013; Medina, 2015).

Causes of shortages

There is now a substantial literature which examines the causes of DS in developed countries. The EMA (2012) groups these into three broad categories: 1) economic and regulatory reasons, 2) business reasons and 3) manufacturing and supply chain problems. Economic and regulatory causes of DS include: issues arising from austerity, restrictive fiscal policy and related government policy changes; increasing regulatory requirements; and shift in demand due to new therapeutic applications. Business reasons contributing to DS include: increasing price volatility; reduced margins; increasing dominance by a limited number of producers; parallel sales; tendering systems which favour larger scale producers; and the impact of medico-legal considerations. Lastly, some of the key manufacturing problems associated with DSs relate to problems in adapting to increasing governmental requirements; transfers of production due to mergers and acquisitions; long production lead times; increasing raw material bottlenecks (active substances, excipients); quality-related failure of production batches; and multi-authority approval requirements arising from outsourcing practices (IMS Health 2015, 2011).

A review of this literature highlights the intertwined nature of a number of underlying triggers. These include complex global supply chains (EMA, 2012, p. 3), production system issues (ISPE, 2014; Ventola, 2011), market demand and production planning (Saedi, Kundakcioglu & Henry, 2016), poor market attractiveness (Gupta and Huang, 2013), fiscal policy and pricing mechanisms, and compliance and quality issues (ISPE, 2014; Ventola, 2011). Industry concentration also emerges as an underlying driver of many 'business reasons' (Weaver, 2010). It appears that concentration, in turn, is linked to the 'end of patent' status of certain drugs and the introduction of generics, with concomitant price reduction and resultant product portfolio decisions influencing supply. This seems to be compounded by tendering processes that favour larger suppliers (IMS Health, 2015). While some causes, such as quality and compliance issues, may be reduced through good practice (FDA, 2013; Pew Charitable Trusts and ISPE, 2017), the intertwined nature of a range of causes contributes to increasing uncertainty of supply. This suggests that only a holistic response will be successful which involves coordination among, or at least consultation with, multiple stakeholders (van Bueren, Klijn & Koppenjan, 2003).

Emerging policy responses

The first formal high-level regulatory response to pharmaceutical shortages was the US Executive Order 13588 on reducing prescription DS of 2011 (The White House, 2011). This legislative intervention instructed the FDA to broaden reporting of potential DS, expedite regulatory reviews and examine whether potential shortages have led to price gouging; while earlier proposals for more hands-on interventions such as creating a national stockpile of drugs or addressing pricing issues in order to alleviate shortages were not followed up (see e.g, Chabner, 2011). Further acts included the US DS Prevention Act of 2012 and the Food and Drug Administration Safety and Innovation Act (FDASIA) which allowed for the extension of expiry dates and a relaxation of import regulations (FDA, 2013). More limited measures had been introduced in Germany in 2009, such as amendment 15 to the AMG (medicines law) which focused on manufacturer and wholesaler responsibilities to maintain adequate stock and supplies (Preuschhof, 2009); and this is mirrored by Austrian regulations (AGES, 2017). Since 2011, Spanish governmental authorities have undertaken measures to limit the export of medicines from the domestic market due to European parallel trade, but this seems to have had only limited success (Leopold et al., 2014). No comparable legislative measures have been adopted in Ireland (IPU, 2017).

Classification of Policy Responses

Methodology

One of the main responses to DS has been the creation of shortages lists by government ministries or arms-length organisations. As previously indicated, these lists differ in terms of processes of identification, ownership, and ultimately, the objectives which motivate data collection. Table 1 below, includes summary data for a number of jurisdictions for which there is a level of comparability. The data was collected by the authors on the 12th to 13th of July 2017 from the webpages of agencies that have a recognised responsibility for collecting this data for their respective jurisdiction. Specifically, jurisdictional data were derived from the following sources: for Europe—the European Medicine Agency; for the US—the Federal Drug Administration (FDA); for Germany—the Federal Institute for Drugs and Medical Devices, (BfArM in German); for Spain—the Spanish Agency of Medicines and Medical Devices, (AEMPS in Spanish); for Austria—the Federal Office for Safety in Health Care, (AGES in German); and for Ireland—the Irish Pharmaceutical Union (IPU). In order to account for the fact that some countries excluded vaccines and veterinary medicines while others did not, which would adversely affect data comparability, these were excluded from the analysis for all countries.

Exploratory Empirical Findings

According to this snapshot, the largest number of DS was listed by Spain's AEMPS with 215 shortages, followed by the Irish IPU with 127 drugs. Next came the US FDA with 60 listed shortages followed by the Austrian and German health agencies with a near identical number of 28 and 27 shortages respectively. Coming last, the European Medicines Agency (EMA) listed only 8 DS.

Table 1: Number of DS listed by jurisdiction/organisation on 12th/13th of July 2017

Jurisdiction (Organisation)	**Current Shortages***	**Resolved Shortages***
Europe (EMA)	8	8
US (FDA)	60	18
Germany (BfArM)	27	-[+]
Spain (AEMPS)	215	-[+]

Austria (AGES)	28	21
Ireland (IPU)	127	19

* excluding, for all countries, vaccines and veterinary medicines which were variously included or excluded by individual national/regional shortlists.
+ information not provided.

Some of these differences are directly attributable to variations in the objectives underpinning data collection. The EMA bases its reporting on information received from member states and only identifies a European shortage when more than one state has reported a drug as being unavailable (EMA, 2013). The FDA, meanwhile, monitors manufacturers and collates information provided by them. It identifies shortages when, based on information from all manufacturers, the market is not covered. The market is considered covered when supply is available from at least one manufacturer to cover total market demand, which does not preclude the possibility that some manufacturers may not have all presentations available (FDA, 2011). The German regulator also bases its list on information provided by manufacturers, but supplements this with data from a federal information system. There is a requirement on industry to inform BfArm on drugs where the number of license holders, the end-user producer or the active substance producer, falls below a critical limit for a particular active ingredient. BfArM also asks industry to report foreseeable bottlenecks without delay, no later than 6 months in advance (BfArM, 2017). The Spanish regulator, meanwhile, bases its listing on voluntary reports received by both license holders and health authorities (AEMPS, 2017). Similar to Germany, Austria relies on a mix of voluntary reporting by license holders and legal requirements for this to take place in case of essential medicines (AGES, 2017). The Irish Pharmaceutical Union, lastly, has perhaps the most liberal approach to shortages by relying on the voluntary contributions of manufacturers and suppliers (IPU, 2017), with no governmental involvement.

The high count of 215 shortages for Spain can be partly attributed to the fact that this includes clinically essential as well as non-essential pharmaceuticals. This is mirrored by the Irish approach which gives similar information to the Spanish listing, but sorts shortage drugs by manufacturer—without giving additional information on the therapeutic use of drugs, as provided in the Spanish listing. Both approaches contrast with the Austrian and German listings which, at the time of our analysis, listed only hospital-relevant and/or essential drugs with a focus on active

ingredients. The US approach seemed to fall between these two extremes in that this DS listed active ingredients and also identified specific brands with a focus on drugs which have been identified as clinically relevant by a government agency.

The underlying reasons for these different approaches are difficult to disentangle. In some sense the Spanish approach and even more so the Irish approach seems to lie at the lower end of regulatory input (or administrative reach) in that any medication which is unavailable can enter the shortage list. This would perhaps be expected in the case of Ireland, as this is the only jurisdiction in this sample where a DS list is provided by a voluntary professional organisation rather than a ministry. However, this logic would obviously not apply to Spain where the DS list is compiled by a branch of the health ministry. The German and Austrian approaches, by contrast, require a higher degree of regulatory input which focuses on active ingredients or components whose absence could lead to a shortage of hospital relevant or essential drugs. As such these two approaches appear to prioritise public health concerns and their centralised management, while potentially paying less attention to the immediate information needs of users. This again could be seen as an expected outcome as, in both cases, branches of the respective health ministries own, collate and manage these lists together with providing a host of supplementary information. Matters in the US are complicated with regard to ownership, with the FDA controlling and compiling a shortage list, while the ASHP plays a key role in advising healthcare practitioners with clinically relevant information including data on potential substitutes.

Each of these approaches, needless to say, has advantages and disadvantages. The Spanish and Irish approaches give a largely unfiltered picture of specific product types which community or hospital pharmacies cannot obtain. This may be useful for healthcare practitioners who seek to verify whether a shortage they encounter affects the country more broadly. The US, and to a greater degree Germany and Austria, by contrast, focus on clinically essential drugs. In the case of the US information is presented primarily from a therapeutic perspective, with a focus on shortages for which there is no immediate substitute and which therefore could adversely affect the health outcomes of patients. The German and Austrian regulators seems to have approached the management of their lists from a similar perspective,

while focussing additionally on shortages from the perspective of the ingredient availability level. This is similar to the EMA approach which additionally imposes the criterion of multi-state unavailability.

It stands to reason that engagement with DS at the therapeutic level is particularly useful where a regulator seeks to encourage the adoption of mitigation strategies which focus for instance on the identification of alternatives, the extension of expiration dates or similar measures. A focus on the ingredient level, lastly, appears to be reflective of a broader, long term public policy lens, where efforts are made to centrally identify potential future at-risk medicines and to remedy root causes accordingly.

The level of institutional engagement with shortages as a policy issue is also reflected in the way designated jurisdictional organisations provide supplementary information as part of DS lists—albeit that the relationship is not absolute. This is illustrated by Table 2 below which again is based on data collected on the 12th and 13th of July 2017 for the same set of countries and organisations as shown in Table 1. According to this analysis, most countries provide information on the active ingredient of shortage drugs. The only exceptions to this are the Spanish and Irish listings. In both instances, some of this information may be available via the interface of a number code— which in the Irish case represents a reimbursement number. Only a small number of countries—namely the US, Germany and Austria—give contact details of manufacturers and suppliers of DS pharmaceuticals; and only two countries—Germany and Austria—provide information on potential future shortages.

Table 2: Characteristics of, and supplementary information given by, DS lists on 12th/13th of July 2017

Country	Active Ingredt	Producer /Market Authristn Holder	Prodcer Contact Details	Short -age Start	Expected/ Actual Shortage End	Potential Future Shortages	Brief Comment	Explanatory Comment Incl Causes/ Reason	Therapeutic Class/ Uses	Link to Detailed Medicines/ Therapeutic Information	Therapeutic Alternatives	Patient Info
EMA	X	-	-	X	-	-	-	X	X	X	X	X
US	X	X	X	X	X	-	X	X	X	X	-	-
Germny	X	X	X	X	X	X	X	X	-	-	X	-
Spain	-	X	-	X	X	-	-	X	X	X	X	-
Austria	X	X	some	-	X	X	X	X	-	-	-	-
Ireland	-	X	-	-	X	-	X	X	-	-	-	-

While definitional difference make comparisons difficult, other studies would suggest that Spain and Ireland, which we identified as the European jurisdictions listing the most pharmaceutical shortages have indeed been particularly hard hit by DS (Costelloe et al., 2015; Pauwels et al., 2014). This contrasts with Austria and Germany, which we show as listing a relatively small number of DS and which past research has identified as being less affected by these pressures (Leopold et al., 2014). No comparable conclusion, meanwhile, can be drawn for the EMA as definitional differences are too pronounced. The US position in between the extremes of low German/Austrian and high Spanish/Irish DS figures reflects a reality of limited successful engagement with DS management.

Analysis

Within this small sample of countries, overall DS management approaches seem to be distinguishable along two dimensions (see Figure 1). The first is the level of salience attributed to DS, with the EMA, Spain and Ireland attributing relatively little urgency or prominence to DS as policy issue; and Germany, Austria and the US giving DS major attention, The second is the level of active state involvement with DS, with the state acting as major policy maker and driver in case of the EMA, Spain, Germany and *Austria*; and the state delegating functions to private agencies and playing a relatively limited role in the case of Ireland and, perhaps to a lesser degree, the US. Accordingly, we find the least developed levels of DS policy among jurisdictions of the 3rd quadrant (Ireland) where both salience and levels of state engagement are low. More evolved levels of DS policy are found in jurisdictions of the 1st quadrant (EMA, Spain) where salience is low, but level of state engagement is more pronounced. A further step up in terms of the development of DS policy can be found for the 4th quadrant (US) where salience is high but levels of active state engagement relatively low. Lastly, we observe relatively highly evolved DS policies for 2nd quadrant jurisdictions (Germany, Austria) where both salience and levels of active state engagement are high.

Figure 1: Key Dimensions, and jurisdictional types, of DS policy

Nature of State Policy Making in relation to DS	*Level of Salience attributed to Drug Shortage*	
	Low	High
Active state (high levels of administrative involvement/commitment; limited delegation)	(1) **EMA, Spain** -state does not negotiate, broker, or become actively involved -state does not regulate -state monitors -state provides research & -advice on clinical alternatives/solutions -state does not delegate	(2) **Germany, Austria** -state actively negotiates, brokers deals manages stakeholder involvement -state is reluctant to regulate if problems can be resolved as above -state monitors -state provides research & -advice on clinical alternatives/solutions -state does not delegate
Passive state (low levels of administrative involvement/commitment; high levels of delegation)	(3) **Ireland** -state does not negotiate, broker or become actively involved -state does not regulate -state does not monitor -state delegates monitoring to professional association -clinical advice is not provided	(4) **US** -state does not negotiate, broker or become actively involved -state regulates -state monitors -state delegates advice on clinical alternatives to professional association

These broad policy differences are closely mirrored by the conceptual strategic orientation of DS policy within these jurisdictions; whereby the level at which shortages are perceived, the key perspectives adopted, the time frame toward which solutions are geared and the nature of the response are closely related (Table 3). Accordingly, in Ireland and Spain, DS are detected at the individual product level with individual prescribers playing a major role, while attempts at resolving these problems are largely ad hoc and short term in nature, being typically designed as a reaction to problems as they arise. In the US by contrast, the focus of DS management is on the level of therapies and this thinking guides the identification of shortages, while policies focus on the medium term of problem resolution and risk mitigation. The German and Austrian approaches, lastly, seek to identify shortages at the active ingredient level, emphasise long-term solutions and are focused on prevention.

Table 3: Conceptual Framing and Strategic Orientation of DS Policies

Level at which DS is perceived:	*Perspective is driven by:*	*Timeframe of solution is:*	*Strategic approach is:*	*Example*	*Country*
Individual product level	Prescriber	Ad hoc/ Short term	Reactive	Examine, ration, reallocate existing stocks; attempt to buy from market	IE; ES
Therapeutic level	Pharmacy/ Pharmacy system	Medium term	Mitigating	Extend expiry date; find alternative sources; risk assess therapeutic alternatives	US [FDA & ASHP]
Active Ingredient level	Health Care system	Long term	Preventative/ Forward looking	Ensure production of active/source ingredient by multiple suppliers	DE; AT

Figure 1 and Table 3, obviously contain an element of simplification, if only because this static analysis does not adequately reflect policy changes and dynamics within each jurisdictional unit. However, the proposed classification is supported by a number of observations at different levels, and therefore can serve at least as a temporary, cross-sectional typology of DS policy.

Discussion

Our analysis confirms the existence of strong path dependence in the adoption of policy responses (Béland, 2010; Feder-Bubis & Chinitz, 2010) which we find manifest in a pronounced typology of pathways where jurisdictional approaches to pharmaceutical shortage management differ along two core dimensions: namely, the salience attributed to the problem and the level to which state organisation engage with the problem. Specifically, we find the US to have attributed a high level of salience to DS while maintaining a relatively low level of direct state involvement in their management. This contrasts with Germany and Austria where levels of salience attributed to DS are also high, but where additionally the state has adopted a direct and active role in their management. For the EMA and Spain, we identify a relatively low levels of salience in terms of DS problem characterisation, while state organisations maintain a direct and active role in monitoring and the provision of advice on alternatives and substitutes. Ireland

represents a case of delegation to a weak arms-length professional organisation where DS are given low salience and state involvement in their management is virtually non-existent. These patterns are mirrored in the conceptual framing and strategic orientation of the respective DS policies, with Spanish and Irish DS policies focusing on the individual product level and being largely reactive; US policies focusing on the therapeutic level with a focus on mitigation; and German and Austrian policies seeking to address the active ingredient level with a focus on shortage prevention.

Conclusions

This paper has sketched out divergent patterns of policy making in relation to the novel and evolving problems of DS. Overall these patterns exhibit strong characteristics of path dependence, with the US approach to DS management reflecting a preference for small government, delegation and legislative solutions; and the German and Austrian approaches signifying a preference for an active, state-resourced involvement of ministries in DS management. This mirrors observations made in connection with the now well-established strong or weak state literature (Atkinson & Coleman, 1987), which observed that these concepts are most appropriately applied to the sectoral level, such as health policy, as some states can be weak in some areas and not in others. At first sight then, these divergent policy preferences are not new, with the literature on path dependence having highlighted a strong role of legacies in health policy making in particular. Despite the importance of legacies, we find evidence of innovation particularly in relation to the US and German approaches which we explain on the basis of Djelic & Quack's (2007) prediction that perceived internal crisis can lead to path creation, particularly where external pressures relate to local stakeholders (Djelic & Quack, 2007; Jacobs & Weaver, 2015).

Thus, in the case of the US delegation is pronounced in that core DS management and communication activities are increasingly resourced and performed by a professional organisation—the ASHP—which, in conjunction with the University of Utah, is providing many functions the FDA is not resourced or equipped to provide (Fox et al., 2014). This collaboration, however, is also novel in that it involves close cooperation, communication and co-ordination between the two organisations. Accordingly, this evolving collaboration involves a pattern where information is routinely shared between the FDA and ASHP for posting on the websites of both organisations, while the ASHP is

given a wide remit for providing therapeutically and practitioner relevant information for healthcare providers and patients (Fox et al., 2009).

In the German case, meanwhile, the innovation and path creation centres on the jour fixe arrangements introduced in 2013. As a semi-formal meeting of key stakeholders, this involves representatives from a number of permanently participating organisations, including manufacturing, prescribing and overseeing bodies, as well as federal state representatives (BfArM, 2016). While this approach to problem solving or crisis management could be seen as borrowing from the neo-corporatist 'konzertierte Aktion' approaches utilised in the context of economic policy making (Schlecht, 1968) and later in health policy making (Wiesenthal, 1981), its application to DS seems to far closer to network governance than the negotiation centred orientation of earlier fora (BfArM. 2016).

Common to both the US and Germany is a widely-shared perception of DS as a major national crisis (Fox, 2014; BFrAM, 2016). This has been driven, in part, by strong professional organisations in the healthcare sector who have problematised DS as an urgent national policy issue. In both jurisdictions clinical professionals have acted as key voices and informers to the public and to governmental organisations. Simultaneously, insurers, hailing either from the heavily individualised US private systems, or the increasingly outcome-focused and competitive semi-state German insurance systems have demanded action on this issue. Meanwhile, in both cases, existing parameters of health care problem-solving have revealed themselves to be inadequate. This has engendered creative solutions in both jurisdictions, though the German jour fixe arrangement and the comparable approaches of Austria are arguably more holistic and further developed. Reflecting a US preference for small government, reliance on the ASHP offers temporary advantages, but lacks potentially both in term of holism and long terms financial sustainability.

Spain and Ireland so far have experienced a low prioritisation of DS as health problem. This may be due to such factors as a recent past of severe austerity (Leopold et al., 2014) and, in the case of Ireland, a high degree of fragmentation of the health system, combined with a significant national economic reliance on the pharma industry (Turner, 2015). Most interestingly, the EMA also seems not have embraced the more advanced approaches

developed by the US, Germany and Austria. This could be due to it holding a number of mandates with DS management being deprioritised in favour of its role in drug authorisation (Gehring and Krapohl, 2007).

Given the exploratory nature of this paper, it may be worthwhile for future research to examine in greater detail the drivers and obstacles which have shaped jurisdictional responses to this important and ongoing contemporary policy challenge. A number of researchers have, like us, investigated initiatives and approaches to the problem of DS (Bochenek et al 2018, De Weerdt et al 2017), and it is likely that the ongoing complexity of the issue will engage researchers for some time.

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