Introduction 1

1.1 Background and Terms of Reference

Healthcare is a major component of the contemporary welfare state, and thus ensuring public health through product safety is a substantive public concern.

It is universally accepted that all medicines might produce adverse drug reactions (ADRs) during the course of their normal therapeutic use (Belton and the European Pharmacovigilance Research Group 1997). In order to ensure post-marketing authorisation safety, all suspected ADRs must be reported in an accurate and timely manner.

Due to the use of living cells, biological medicinal products (so-called biologicals) pose a specific challenge for pharmacovigilance and the accurate reporting of ADRs for mainly four reasons: restrictions in clinical trials, sensitivity to changes in the manufacturing process, reporting of batch numbers and the establishment of valid causality assessments.

For these reasons, the timely and accurate reporting of ADRs is particularly important when it comes to the use of biological products. In order to ensure the correct and timely attribution of adverse events to the correct biological product and batch, the availability of information such as the international non-proprietary name, the brand name, the company's name and the batch number are extremely important.

The former European Union (EU) pharmaceuticals legislation (Directive 2001/83/EC) underwent an extensive reform process since 2006, which resulted in a new Directive (2010/84/EU) and Regulation (No 1235/2010) in 2010, bringing about significant changes to pharmacovigilance in general and ADR reporting in particular.

The new legislation, in force since July 2012, strengthens the monitoring of medicinal products in general and biologicals in particular to ensure public health through product safety. The new legislation is geared towards the detection of adverse reactions to medicinal products that have been authorised for marketing,

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and it consists of activities and methods for detecting, assessing, informing on and preventing ADRs.

In August 2016 the European Commission (Commission) published its assessment of the new EU pharmacovigilance legislation. The assessment consists of two documents, namely the Commission Report titled "Pharmacovigilance-related Activities of Member States and the EMA Concerning Medical Products for Human Use (2012-2014)" and the related Commission staff working document. The first document, an eight-page report, mainly explains the role of the relevant actors involved (Member States, EMA and the Commission) and the main activities related to pharmacovigilance. Further, the report provides statistics on the numbers of pharmacovigilance-related reports and activities between 2012 and 2014 (such as ADR reports), showing that the situation in Europe has been steadily improving since the adoption of the new pharmacovigilance legislation. The Commission staff working document is more elaborate (54 pages) and includes additional information on activities related to ADR reporting, such as improvements in strengthening patient involvement or awareness-raising campaigns (European Commission 2016, 10-12).

Both Commission documents, however, only scratch the surface and do not go into further detail about the overall day-to-day functioning of the pharmacovigilance systems in single Member States, the remaining challenges, or factors that might impede or incentivise ADR reporting. Most important, they lack country-specific and detailed information about the ADR reporting of biologicals.

This also holds for the work conducted by the three-year Joint Action, called the "Strengthening Collaboration for Operating Pharmacovigilance in Europe" (SCOPE, 2013-2016). Funded by the Consumers, Health and Food Executive Agency,[1] this collaborative joint action was created to support effective implementation of the pharmacovigilance reform. SCOPE aims at delivering practical tools to and guidance for nation regulatory authorities to ensure the consistent development of pharmacovigilance systems across Europe, including training in key aspects of pharmacovigilance and tools and templates that aim to support best practices across Europe. SCOPE was divided into eight separate work packages, one of which focused on improvements in ADR reporting.

Overall, SCOPE offers a useful source of information for horizontal aspects of national pharmacovigilance systems in Europe. It provides a fuller general understanding of, and develops best practices in, reporting mechanisms for ADRs.

However, SCOPE pays little attention to biologicals. Moreover, its survey data does not allow tracing back country-specific information. Therefore, SCOPE does

1 Executive agencies in the EU are created by the Commission to support the implementation of specific programmes, inter alia, in the area of public health.

not contribute to a Member State-specific understanding of reporting mechanisms for ADRs regarding biologicals.

In summary, our study focuses on the ADR reporting of biologicals and on specific EU Member States representing various types of healthcare systems across Europe. Assessing the timely transposition and accurate implementation of the European pharmacovigilance framework as described in Directive 2010/84/EU, this report aims at identifying major drivers impeding and incentivising appropriate ADR reporting in Europe. Our assessment offers a rich and detailed account of ADR reporting systems across individual Member States, identifying perceived challenges and best practices in order to formulate recommendations on the necessary conditions for robust and effective systems ensuring accurate identification and rapid traceability of biological medicines.

1.2 Methodology: Selection of Countries

Assessing medical services has become a political issue throughout the industrialised world. The utilisation of health services is influenced by the activities of physicians, hospitals, professional associations, interest groups, legislative chambers and administrators. Furthermore, it is influenced by the competition of rival ideologies. Thus, systems can be centralised or decentralised, or possibly fragmented in a recentralised state.

Therefore, our research strategy for the EU pharmacovigilance implementation project goes beyond single-country studies. Its geographic scope covers six areas, distinguishing between ideal systems – namely, state healthcare systems and societal healthcare systems (as well as various permutations of mixed systems thereof):

- United Kingdom (ideal-type state healthcare system)
- Finland (state-based mixed type)
- Poland (state-based mixed type)
- France (state-based mixed type)
- Portugal (societal-based mixed type)
- Germany (societal-based mixed type)

Essentially, there are three responsibilities in healthcare: first, the financing of health services through taxation, social insurance contributions or private means; second, the provision of healthcare which can be carried out in state-run facilities by state-based actors, in societal-based facilities, or in private for-profit facilities

by private actors; and third, the regulation by these actors of the various aspects of financing and provision (Moran 1999; Burau and Blank 2004). Taken together, the financing, service provision and regulation of healthcare are three key dimensions along which different groups of actors may take on numerous roles and exhibit varying levels of engagement. However, in "real" medical care systems, the "state", "societal" and "private" elements tend to coexist alongside each other in all three dimensions. Therefore, when analysing changes over time, the mix within categories is taken into consideration.

Based on uniform features across all dimensions of healthcare, we identified three instances of ideal types. These types comprise state healthcare systems, in which financing, service provision and regulation are carried out by state actors and institutions; societal healthcare systems, in which societal actors take on the responsibility of healthcare financing, provision and regulation; and finally private healthcare systems, in which all three dimensions fall under the auspices of market actors.

In total, six empirical cases illustrate different arrangements for governing the medical care sector and their associated political problems. The United Kingdom, Finland, Poland, France, Portugal and Germany have different public traditions concerning the ratio of individual versus collective responsibility for social welfare in general and medical care in particular.

Given their respective histories and patterns of development, Finland and the United Kingdom have well-developed prototypes of organisational and political arrangements. The United Kingdom is highly centralised and its National Health Service (NHS) is directly financed by the central government out of general tax revenues. Significant changes have taken place intra-dimensionally such that there has been an internal shift of levels. The introduction of an internal market in the United Kingdom has not led to a replacement of the state as the main regulator; however, the United Kingdom has created some space for self-regulation through NHS trusts. Finland, although a unitary state, has granted important financial and organisational roles to local authorities, and it has decentralised many health-related functions to regional levels.

Germany can be characterised by predominantly social-insurance-based regulation and financing combined with a high and increasing share of private healthcare provision. In addition, the current growth of state intervention in Germany even enlarges the distance to the societal-based ideal type.

Poland is exemplary for Central and Eastern Europe which has changed from socialist healthcare systems to social health insurance systems (Dubois and McKee 2004) and is currently characterised by comparatively weak social insurance systems actors and a high proportion of healthcare being provided in public hospitals.

Despite the low level of tax funding, Poland can still be classified as the state-based mixed type, and only a strengthening of corporate social insurance actors would lead to a real system change.

Southern European countries changed from a social insurance type to a national-health-service type in the late 1970s and early 1980s (Guillén and Matsaganis 2000). In contrast to France, however, Portugal maintained elements of the former social health insurance scheme and is characterised by weak public authorities (Cabiedes and Guillén 2001).[2] Despite the weakness of state authorities, the changes of the 1970s and 1980s seem to represent a system shift from a societal-based mixed type towards a state-based mixed type (Wendt et al. 2009).

1.3 Methodology: Research Strategy

The primary assessment program involves a range of research methodologies that are both quantitative and qualitative. Based on a mainly threefold methodological approach, including qualitative, quantitative and benchmarking methods, the findings and recommendations have emerged from a most appropriate, sequential desk and field research process, benchmarking, and interviews across the six selected Member States, national (hospital) pharmacist associations, national regulatory agencies, and those administering systems for post-marketing safety surveillance of biologicals, including spontaneous reporting systems and external stakeholders.

The research strategy for the EU pharmacovigilance implementation project comprises five key stages, as outlined below and detailed in the following paragraphs:

- Desk-based analysis
- Document research
- Key informant interviews
- In-depth field research
- Benchmarking

Desk-based analysis. There is a vast literature on pharmacovigilance dealing with incentives of healthcare professionals to report ADRs. This literature was crucial for developing analytical categories for both desk-based and field-based research. However, given that this literature is part of the health sciences, it is concerned

2 Spain, in contrast, has experienced reforms of the medical care sector which means that it no longer has a societal-type system.

primarily with individual factors of ADR reporting, and it necessarily neglects political implications at the systems level. Furthermore, research designs are mostly based on surveys conducted in single case studies, and thus deal with countries in isolation. Extending on this literature, the six empirical case studies, based on varying organisational and political arrangements, allow for a better contextualisation of ADR reporting.

A comparative case study, with cases selected on an ideal-type health system, provides for added benefit to the existing literature.

Document research. Assessing the transposition of the European pharmacovigilance framework involved conducting a documentation review. This first phase helped collect useful information on the timely and correct transposition, management and governance of compliance with Directive 2010/84/EU across all EU-28 Member States. Information on the EU pharmacovigilance Directive was taken from the official legal database of the EU, which covers all Member State legislation and provides publication references regarding Member States' national provisions to enact EU legislation. Because Member States often transpose EU legislation by using more than one national transposing instrument, we recorded all transposing instruments that were indicated to the Commission until March 2016. Because the recorded measures do not indicate whether the national implementation process is complete, a second step was put in place.

Key informant interviews. It is essential that practitioners, industry and regulators participate in the reporting of suspected ADRs in order to ensure accurate traceability back to the manufacturer. Consequently, formal schemes were established in every country to enable healthcare professionals and the public to report ADRs.

This step involved a series of in-depth interviews which were carried out, either face-to-face or by telephone, with different stakeholder groups to map the national pharmacovigilance systems. We developed a list of potential interview partners who would be relevant for the study, and from this list of stakeholders, we conducted 33 key informant interviews with executives, healthcare professionals, the industry and patient organisations between April and September 2016.

On the basis of these interviews, the country chapters mapping the respective national pharmacovigilance systems were finalised and a first set of perceived best practices and challenges was drafted.

In-depth field research. The third step in assessing the European pharmacovigilance framework as described in Directive 2010/84/EU involved in-depth study and visits

to the six selected countries. This step also helped us compare the different national systems and develop recommendations.

Simultaneously, monitoring data provided in documents, websites and reports reflecting the current state of play of academic literature was performed. This has included collecting details on the number and features of adverse drug reporting, incurred by the following studies:

- Andrews, E., Moore, N. (eds) (2014). *Mann's Pharmacovigilance*. Wiley-Blackwell Oxford.
- Drozd et al. (2014). *Biosimilar Drugs – Automatic Substitution Regulations Review. Polish ISPOR Chapter's Therapeutic Programmes and Pharmaceutical Care (TPPC) Task Force Report*. Journal of Health Policy 1: 52-57.
- European Commission (2016). *Pharmacovigilance Related Activities of Member States and the European Medicines Agency Concerning Medicinal Products for Human Use (2012-2014),* COM(2016) 498 final, Brussels, 08.08.2016.
- SCOPE (2016). *Work Package 4 – ADR Collection*.
- Vermeer et al. (2015). *Traceability of Biologicals: Present Challenges in Pharmacovigilance*. Expert Opinion on Drug Safety 14 (1).

Benchmarking. Benchmarking analysis included a comparative assessment of cases highlighting perceived best practices versus perceived challenges in developing national systems, allowing for the identification of biologicals by brand name and batch number.

By utilising these comparative materials, we were able to see the relative strengths as well as the chronic problems of the EU pharmacovigilance system. Drawing on desk- and field-based research, these findings complement and add significantly to primarily theoretical discussions about the system (see Borg et al. 2015; Calvo and Zuñiga 2014). The research distinguishes the malleable from the inevitable in health-related decision-making across Europe and thereby suggests the constrained nature of policy options in Western democratic societies.

1.4 Summary of Evidence

This study presents our findings and conclusions that were formed by assessing all of the elements in the cumulative process described here. Additional interviews were conducted to validate the emerging conclusions that we reached from the benchmarking analysis and field and desk research. We weighed all evidence equally, except when the evidence was clearly unrepresentative or not credible. In cases where we do not provide specific evidence to support a finding or conclusion, it is because we have combined the evidence to present a summary conclusion. The recommendations are based on our own analysis.

1.5 Implementation Assessment Structure

The main purpose of this EU pharmacovigilance implementation study is to present the findings of the comparative assessment of six national ADR reporting systems for biologicals and to outline recommendations for future action. After having put the implementation assessment into context and taking into account the complexity of the study through a threefold methodological approach, we determined six important goals, corresponding to the following structure of the manuscript:

- Chapter 2: Pharmacovigilance. This chapter outlines the fundamentals of pharmacovigilance with a particular emphasis on the role of healthcare professionals when it comes to ADR reporting. The chapter also explains why pharmacovigilance is specifically important regarding biologicals.
- Chapter 3: The EU Pharmacovigilance System. This chapter outlines the main objectives of pharmaceutical regulation in the EU, tracing the developments in terms of pharmacovigilance. It identifies the complex network of EU actors and presents the key features of the current EU pharmacovigilance system. In addition, this chapter also presents in detail the reform of Directive 2010/84/EU and how it aims to facilitate ADR reporting in general and biologicals in particular.
- Chapter 4: Timely and Correct Transposition of Pharmacovigilance across Member States. This chapter offers a first assessment of the timeliness of national transposition processes for all EU Member States and shows that many countries have a serious transposition problem in their national pharmacovigilance systems. Unfortunately, it appears that the EU transposition deficit is more than just a statistical illusion. Almost 85 percent of the national transposition instruments are not transposed on time, and in fact are delayed up to more than two years.

Cross-country variance is significant, and the difference between the laggards (Denmark and Slovenia) and the champions (Cyprus, Romania, Sweden, Estonia, the United Kingdom and Ireland) is remarkable.

- Chapter 5: Practical Implementation of Pharmacovigilance in Six Member States. The aim of this chapter is threefold. First, it offers in-depth explanations of the ADR reporting systems, and describes relevant tasks and actors involved in the United Kingdom, Finland, France, Poland, Portugal and Germany. Second, it presents remaining challenges and best practices for each case as perceived by the interview partners. Third, it provides first recommendations on how to improve the existing systems in order to improve ADR reporting and help ensure public health.
- Chapter 6: Challenges and Best Practices in Perspective. This chapter offers an analysis of the findings presented in Chapter 5. Here, the six different ADR reporting systems are directly compared and the remaining challenges and best practices put into perspective.
- Chapter 7: Conclusions and Recommendations. This chapter summarises the main findings that have emerged from the EU pharmacovigilance implementation assessment. On the basis of the results, the chapter outlines specific recommendations in relation to the provisions of Article 2 of Directive 2010/84/EU. Drawing on these specific recommendations, the chapter puts forward general recommendations in the context of national healthcare systems, suggesting the constrained nature of policy options in Western democratic societies. This policy context is crucial for understanding questions about pharmacovigilance and its challenges for practical implementation across Member States.

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