

Exposé

**Analysis of pharmaceutical legislation in Poland with
special emphasis on drug safety**

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1 INTRODUCTION

On 1st May 2004 Poland became a member of the European Union (EU). For Poland, as a post socialist country still in transition, accession to the EU has been a major step in the process of extensive changes concerning the polish legal system. The Accession Treaty requires Poland to adapt its national legal system to the *aquis communautaire*, the entire body of legislation of the EU. Therefore, also the national pharmaceutical legislation has to comply with the EU pharmaceutical *aquis*. In contrast to regulations that are directly applicable in each member state, directives require a transposition into national law and thus, play an important role in the approximation of laws within the EU. Exact execution of the EU requirements is essential to fulfil the objective of uniform standards for medicines throughout the EU and to ensure the surveillance of drug safety [1].

Poland with its population estimated at 38,1 mio. is the sixth most populous member of the EU and a large, dynamically developing pharmaceutical market with a total value of € 6.9 bn in 2009 and a total amount of approximately 9226 medicines registered [2,7]. Thus, Poland is an EU member with considerable value, both with regards to a large consumer market and consequently to drug safety aspects.

2 BACKGROUND INFORMATION

2.1 Legal framework regarding medicines for human use

The EU basic legal framework for the authorisation and supervision of medicines for human use is laid down in the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 [3]. In Poland, the basic national legal act concerning medicines is the Pharmaceutical Law (PhL) of 6 September 2001, a comprehensive legal framework comprising provisions in terms of marketing authorisation, standards for manufacturing of medicines, advertising, clinical trials, supervision over the safe use of medicines and pharmaceutical inspection. Moreover, it specifies the requirements for pharmacies and wholesalers [4]. In an attempt to bring Polish regulations more into line with the EU legislation, the amendment of the PhL of 30 March 2007 introduced further provisions for pharmaceutical inspection, good manufacturing practice, good clinical practice and

monitoring of adverse drug reactions, among others. Further, the PhL of 30 March 2007 aimed at implementing several EU directives, as for example [5]:

- Directive 2001/20/EC on the approximation of laws, regulations and administrative provisions of member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- Directive 2004/27/EC, amending Directive 2001/83/EC on the Community code relating to medicinal products for human use
- Directive 2004/24/EC, amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use

However, despite of Poland's explicit efforts to adapt to EU standards, obligations embedded in the EU provisions have not been entirely fulfilled up to date. Among legal acts, which are still not fully implemented into Polish pharmaceutical law is for example the Directive 2004/27/EC, amending Directive 2001/83/EC, that aims at creating a harmonised EU marketing authorisation procedure, the so-called 8+2 (+1) data exclusivity formula comprising an eight-year data exclusivity provision with a two-year market exclusivity provision. Additional one-year extension can be granted when a new therapeutic indication has emerged during the first 8 years. That means, that generic applications for marketing authorisation can be submitted after 8 years, but the product can enter the market first after 10 (or 11) years [6]. Although the harmonization period for the implementation of this directive has already expired on 30.10.2005, Poland has not adopted all the EU requirements yet and a six-year exclusivity period is still currently applied [7].

2.1.1 Marketing authorisation of medicines

In the united European Community, a medicine can not only enter the national market of a member state, but also be available to patients in several or all EU countries simultaneously. Granting marketing authorisation for medicines in the EU can proceed via the centralised authorisation procedure or national authorisation procedures [8]:

- Centralised procedure (CP): the obtained single marketing authorisation is valid in all EU member states (and also in EEA-EFTA countries: Lichtenstein, Norway and Iceland). Certain medicines, as for example for the treatment of diabetes, cancer and neurodegenerative disorders, can fall exclusively under the scope of the centralised procedure [9].
- National procedures: marketing authorisation is valid in the EU country that granted the approval. Further options are possible in order to receive a marketing authorisation in several EU countries simultaneously [3]:
 - Decentralised procedure (DCP): companies can apply for the marketing authorisation in more than one EU country, provided that a medicine has not yet been authorised in any EU country and does not fall within the mandatory scope of the centralised procedure.
 - Mutual recognition procedure (MRP): marketing authorisation granted in one EU Member State can be extended to further EU countries.

The responsible authority for the registration of medicines via the centralised procedure is the European Medicines Agency (EMA), placed in London. In Poland, the national authority responsible for granting marketing authorisations and for supervision over proper quality, efficacy and safety of medicines is „*Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych*“-URPL (Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, further cited as “the Office”) in Warsaw [10]. The Office was established on 1st October 2002, as the result of the merger of the Office for Registration of Pharmaceutical Products and Medical Supplies of the Institute of Medicines and the Main Medical Technologies Center and was directly subordinated to the Minister of Health. Due to the fact that the Ministry of Health was overburdened with control over the office, which also caused artificial prolongation of authorisations for new medicines, a new law came into force on 1st May 2011. Following the international trend towards the establishment of independent agencies, the primary responsibility has now been transferred from the Minister of Health to the President of the URPL. As an independent governmental agency, it can be anticipated that the process of marketing authorisations will be accelerated in future.

2.1.2 Harmonisation period

By signing the Accession Treaty Poland has been obliged to adjust the medicinal products registration dossier to EU requirements (among others by supplementing information on bioequivalence research) in order to secure access to the EU markets. For this purpose Poland was granted the so-called harmonization period until the end of 2008. During the transition period the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products co-operated closely with the German „*Bundesinstitut für Arzneimittel und Medizinprodukte*“ (BfArM) within the framework of the „Twinning project“. BfArM brought its knowledge and expertise into the project to support and co-ordinate the implementation of EU requirements regarding the procedures of marketing authorisation into Polish pharmaceutical legislation. Although the project was highly successful, according to data from the Registration Office, nearly 1500 drugs have not been submitted by marketing authorisation holders for EU-harmonisation and consequently may only stay on the Polish market until their expiry date. This has created a difficult situation, as the group of not-harmonised medicines also includes almost one-third of reimbursed medicines commonly prescribed in Poland [11].

2.2 Drug safety

Nowadays, drug safety is recognised as one of the major global public health issues. Medicines have to respond to the strictest standards with regards to quality, efficacy and safety, as any shortage can have major impact on patients' health. The national regulatory framework concerning drug safety has to comply with the EU initiatives to fulfil the principal goal of equal standards for medicines in the EU.

2.2.1 Clinical trials

Before marketing authorisation for a specific drug may be granted, several clinical trials on humans have to be carried out. These investigations comprise 4 phases (Phase I-Phase IV), which aim at gathering data on drug efficacy and adverse drug reactions, which is further used to establish a risk/benefit ratio [12].

The EU legal framework for the conduct of clinical trials is provided in the Directive 2001/20/EC and further concretised in the Directive 2005/28/EC, the so-called Good Clinical Practice-GCP Directive, concerning ethics and scientific quality required for planning, conducting, recording and reporting clinical trials [13,14].

Poland represents one of the largest clinical trial markets in Central and Eastern Europe with a high growth potential, mostly due to efficient patient recruitment and competitive cost. Around 450 new clinical trials are registered in Poland each year [15,16]. The Polish legislative framework for clinical trials is included in the Act of doctor's profession of 5 December 1996, PhL of 6 September 2001, as amended by the PhL of 30 March 2007 and in several orders of the Ministry of Health. As relevant Polish rules are dispersed throughout several legal acts, this has shown more than once the incoherence of the legal system and lack of transparency, which might have also contributed to the slowly progressing implementation of EU Directives regarding clinical trials, including Directive 2005/28/EC [17,28].

2.2.2 Pharmacovigilance

At the time that marketing authorisation is granted, medicines are available to an incomparably larger population than previously evaluated during the first three clinical trial phases. With the advent of demographic change and the increase of chronic diseases and associated multi-morbidity, patients are exposed to a systematically larger range of medicines that have the potential to interact with each other. Therefore detection and documentation of rare and long-term adverse effects (ADRs) poses a great challenge for both authorisation granting authorities and pharmaceutical companies as well as health professionals [18].

The surveillance of drug safety in the post-marketing phase is attributed to pharmacovigilance. As defined by the WHO, pharmacovigilance is „*the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem*“ [19]. The tragedy of thalidomide had a major impact on the development of pharmacovigilance and focused public attention on drug safety issues. Thalidomide was launched into the market in 1957 and widely prescribed to pregnant women suffering from morning nausea. It was soon associated with teratogenic effects and severe birth abnormalities in children, whose mothers had been prescribed thalidomide [20], causing over 10 000 human birth deformities, which could have been prevented with sufficient patient safety data. The bitter experience with thalidomide contributed to the establishment of the

WHO Programme for International Drug Monitoring in 1968, an international resource for collecting and evaluating adverse drug reactions. Further there have been several other initiatives worldwide, which aimed at elaborating standards for sustainable drug safety, as for example the „World Alliance for Patient Safety“ from 2004 and the establishment of the Expert Group on Safe Medication Practices within the Council of Europe in 2003 [21].

The Polish National Unit for Monitoring Adverse Drug Reactions has been operating since its inception by the Ministry of Health in 1971, within the WHO Programme for International Drug Monitoring. After Poland's accession to the EU, the Pharmacovigilance Unit within the Office (URPL) is closely cooperating with the European Medicines Agency (EMA). Marketing authorisation holders are obligated to have implemented the pharmacovigilance system and also to deliver reports of adverse drug reaction both on spontaneous basis and in form of summary reports to the Pharmacovigilance Unit of the URPL. Reporting suspected adverse drug reactions is compulsory also for health professionals. However, the amount of Polish reports on spontaneous adverse drug reactions delivered to the WHO has been scarce taking into account its population of over 38 mio. Poland submitted only 3,124 reports over 36 years, while Sweden for example, with only 9 million inhabitants, delivered about 100,000 reports [22].

The EU Commission has assessed that adverse drug reactions are responsible for 5% of hospitalisation cases and 5% of all patients hospitalised experience ADRs. Moreover, regarding the most common causes of hospital death, ADRs are positioned at the 5th place [23]. Only efficient collecting and proper evaluation of high quality ADR reports by all member states may lead to conclusions that could contribute to an enhanced patient safety. On this background, great demand for further development of an efficient pharmacovigilance system in Poland is clearly recognizable.

The importance of a robust drug safety system has been most recently highlighted by serious adverse drug reactions reported in Lipobay® (cerivastatine), Avandia® (rosiglitazone) and Vioxx® (rofecoxib) [24,25,26,27]. Lipobay® has been attributed to an increased risk of rhabdomyolysis followed by kidney failure, that led to 52 death cases worldwide and resulted in the withdrawal of this drug from the global market. The producer of Avandia® was accused to hide negative trial results, which showed an increased risk for heart attacks. Further, Vioxx® may have caused around 28 000 heart attacks in the US during 1999-2003 and was therefore subsequently withdrawn from the market. These events resulted in calls for

more reliable pharmacovigilance systems and highlighted the need of implementing further improvements. Intensive discussions in the EU over the past few years resulted in a new EU pharmacovigilance legislation (Directive 2010/84/EU) that will become applicable in July 2012 and amends the Directive 2001/83/EC. Every EU member state is obliged to efficiently implement the new pharmaceutical legislation into national law. In Poland, currently applicable legal rules concerning pharmacovigilance are laid down in the PhL of 6 September 2001, and further also in the order of the Ministry of Health of 17 February 2003 (regarding monitoring of drug safety) and of 6 September 2007 (regarding pharmacovigilance inspection).

3 AIMS OF THE DISSERTATION

In May 2004 EU faced the most significant expansion in its history. In response to the requirements laid down in the Accession Treaty, Poland is obliged to implement the EU provisions into national law with the objective to facilitate uniform standards for authorisation and surveillance of medicines throughout the EU. However, lack of several European measures in the national pharmaceutical legislation has already been pointed out in the past. Therefore, detailed examination of the implementation of constantly changing EU requirements into the Polish national legislation is of greatest importance.

The aim of this dissertation is to carry out a comprehensive study of the Polish pharmaceutical law concerning medicines for human use, with the objective to analyse its compliance with EU requirements. Special emphasis will be put on aspects regarding drug safety, including clinical trials and pharmacovigilance. During the course of this dissertation, strengths and possible shortages concerning the implementation of EU provisions shall be outlined and recommendations aiming at improving the current system shall be provided.

4 TIME SCHEDULE

The time framework of this dissertation will cover approximately 3 years. The following working plan is proposed:

1 year: Collecting all necessary Polish and European legal acts concerning medicines for human use, with special regards on drug safety.

1 1/2 years: Comparative analysis of EU provisions and selected Polish legal acts with emphasis on their strengths and weaknesses.

1/2 year: Preparation of the dissertation thesis.

During these 3 years, several visits to the URPL are foreseen in order to get direct access to the necessary documents and to gain a better insight into the Polish regulatory system.

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