

**Changes in the Field of Pharmacovigilance within the
Scope of the 12th Amendment and the Drafted 14th
Amendment of the German Drug Law and the Related
EU Legislation**

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1. LIST OF ABBREVIATIONS

In alphabetical order:

ADE	Adverse Drug Event
AkdÄ	Arzneimittelkommission der deutschen Ärzteschaft
ADR	Adverse Drug Reaction
AMG	Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz)
ASI	Arzneimittel-Schnellinformation
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BGA	Bundesgesundheitsamt
CCSI	Company Core Safety Information
CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
DAMA	Deutsches Institut für Arzneimittel und Medizinprodukte
EC	European Community
EEA	European Economic Area
EMA	European Medicines Evaluation Agency
EU	European Union
FDA	Foods and Drug Administration
GCP	Good Clinical Practice
GCP-V	GCP-Verordnung
GMG	Gesundheitssystemmodernisierungsgesetz
ICSRs	Individual Case Safety Reports
IMP	Investigational Medicinal Product
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRP	Mutual Recognition Procedure

PASS	Post-authorisation safety study
PEI	Paul-Ehrlich-Institut
PharmBetrV	Betriebsverordnung für pharmazeutische Unternehmer
PIL	Patient Information Leaflet/Package Leaflet
PSUR	Periodic Safety Update Report
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SPC / SmPC	Summary of Products Characteristics
SUSAR	Suspected Unexpected Serious Adverse Drug Reaction
UAR	Unexpected Adverse Reaction
USA	United States of America

*“All Substances are poisons; there is none one which is not a poison. The right dose differentiates a poison and a remedy.”
Paracelsus (1493 - 1541)*

2. INTRODUCTION:

2.1 Medicinal Products and Adverse Drug Reactions

The purpose of medicinal products is, briefly speaking, to alleviate ailments, prevent and heal diseases and to save life. The advancements in science and technology have facilitated the development of highly effective medicinal products for diseases in all areas of medicine. However, every medicinal product is also associated with side effects as suggested by the Greek word “pharmacon”, which also means poison. An active substance used for medicinal products can also cause harm and a substance designated to be poison heal¹. Therefore, despite intensive pre-clinical and clinical research and safety measures, medicinal products can sometimes cause unwanted side effects, which may be harmless to very serious and which may present a risk to the user of the medicinal product. This fact must always be borne in mind by health-care professionals and patients with regards to using a medicinal product and by the pharmaceutical industry with regards to the development and marketing of a drug.

In the field of internal medicine, adverse drug reactions lead to hospitalisation in about 6% of cases and adverse drug reactions lead to up to 100 000 deaths per year in the USA. The direct costs for hospitalisation due to adverse drug effects are estimated to far exceed 1 billion Deutsch Mark per year² (more than half a billion Euro). Therefore, the prevention of adverse drug reactions is necessary for the protection of the patients and is also important for economic reasons. In addition to the advancement in medicine, expectations of patients to have early access to innovative, effective and at the same time, safe medicinal products have also grown³. The media provides patients with information about new medicinal products and these become increasingly and quicker available to the population due to the globalisation and worldwide marketing strategies. For instance, in the EU, centrally approved products (which are normally innovative products) obtain marketing approval in all Member States at the same time. The increase of the Member States from 15 to 25 on the 1st of May 2004 (plus Iceland, Norway and Lichtenstein, which are also members of the EEA), has also lead to an increase of the population with an access to a medicinal product approved by the EMEA. These developments have lead to an increase in the importance of pharmacovigilance and an effective management of the risks associated with medicinal products.

According to the German “Allgemeine Verwaltungsvorschrift zur Beobachtung, Sammlung und Auswertung von Arzneimittelrisiken (Stufenplan) nach §63 des Arzneimittelgesetzes (AMG)”⁴, Artikel 1 Section 3, the risks associated with medicinal products are:

- Side effects, including those that are associated with the interaction of the medicinal product with another medicinal product,
- The development of resistances in anti-infectives, insufficient effectiveness of vaccines,
- Abuse and misuse,
- Habituation, addiction,
- Insufficiently long withdrawal periods for veterinary medicinal products,
- Quality deficiencies; for objects which are medicinal products, also technical quality deficiencies,

- Deficiencies in the inner and outer packaging,
- Deficiencies in the labelling, the Summary of Product Characteristics and Patient Information Leaflet,
- Counterfeit medicinal products,
- Potential risks for the environment due to the use of veterinary medicinal products.

2.2 Pharmacovigilance

The disaster caused by thalidomide in 1958 to 1961, which led to the birth of more than 10,000 of congenitally deformed infants (about 4000 children in Germany)⁵, resulted in first systematic international efforts to address these issues and in the tightening of the laws world-wide for monitoring the risks of a drug before and after marketing authorisation approval. National pharmacovigilance centres were established in a number of countries and continue to be established, now mainly in developing countries⁶.

Before a medicinal product can be sold on the market, it has to go through an intensive process of marketing approval. In this process, national and international regulatory authorities such as BfArM, MHRA UK, EMEA Europe, FDA and WHO assess the documents which have been submitted by the applicant to prove the effectiveness, safety and quality of the medicinal product. A part of the documentation consists of clinical studies, in which not only the effectiveness but also the safety of the drug has been documented.

Unfortunately, it is generally not always possible to detect rare or very rare adverse reactions of a medicinal product during a clinical trial because of the limited number of participants in the trial. Even for more frequent adverse reactions, the occurrence may be limited to single cases in clinical trials, which does not allow a correct analysis of the frequency of the occurrence of these reactions. Besides, certain adverse drug reactions may occur more frequently in patient populations, which were initially excluded from the clinical trials but are commonly treated with the medicinal product later on. In addition, some drug interactions cannot be detected during a clinical trial, because the additional medication used by patients under real-life conditions may differ to that used by the population in the clinical trial. Furthermore, drug interactions may occur with newly developed drugs, which were not available during the clinical trial programme and were therefore undetectable before marketing authorisation.

Because of this, it is important to continue to monitor the safety of every medicinal product (including generic products) during the marketing phase and to continually analyse the risk/benefit ratio of the product. To this end, adverse drug reaction reporting and assessment systems have been set up worldwide to gather signals* of drug safety. Drug safety monitoring or pharmacovigilance therefore plays a major role in pharmacotherapeutic decision-making, be it individual, regional or international⁶.

The word pharmacovigilance is derived from the Greek 'Pharmaco' (medicine) and the Latin 'Vigilantia' (vigilance, watchfulness)⁷. Pharmacovigilance is the science and

* A signal is reported information on a possible causal relationship between an adverse even and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information (Glossary, The importance of Pharmacovigilance (safety monitoring of medicinal products), World Health Organisation 2002, ISBN 92 4 159015 7

activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems⁸. More generally speaking, it is the study of the benefits and risks of drugs⁶.

According to the World Health Organisation (WHO), the specific aims of pharmacovigilance are⁹:

- Detection of increases in frequency of (known) adverse reactions,
- Identification of risk factors and possible mechanisms underlying adverse reactions,
- Estimation of quantitative aspects of benefit/risks analysis and dissemination of information needed to improve drug prescribing and regulation

The ultimate goals of pharmacovigilance are:

- The rational and safe use of medical drugs,
- The assessment and communication of the risks and benefits of drugs on the market,
- The education and informing of the patients
- To improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions,

One of the major tools of pharmacovigilance is *spontaneous reporting*. In most instances it is the only early signalling method available for newly marketed drugs and infrequently used drugs¹⁰.

2.3 The German Pharmacovigilance System

The laws governing pharmacovigilance in Germany are laid down in the German Drug Law* (Arzneimittelgesetz, AMG). These laws are further defined by regulations such as the "Betriebsverordnung für pharmazeutische Unternehmer (PharmBetrV)" and the administrative regulation "Allgemeine Verwaltungsvorschrift zur Beobachtung, Sammlung und Auswertung von Arzneimittelrisiken (Stufenplan) nach §63 des Arzneimittelgesetzes", promulgations such as the 4th Promulgation Concerning Reporting Obligations (4. Bekanntmachung zur Anzeige von Nebenwirkungen, Wechselwirkungen mit anderen Mitteln und Arzneimittelmissbrauch nach §63b Abs. 1 bis 8 AMG), communications, guidelines, etc.

Patients, health-care professionals such as physicians and pharmacists, the drug commissions, the pharmaceutical industry, surveillance authorities (such as the Government of Upper Bavaria) and the regulatory authorities (BfArM or PEI) are the partners in the German drug safety system.

Section 5, sub-section 1 AMG contains a prohibition in respect to unsafe drugs. It states that *the placing on the market of unsafe drugs shall be prohibited*. According to sub-section 2, drugs shall be considered unsafe if, according to the current level of scientific knowledge, *there is reason to suspect that, when used in accordance to their intended purpose, they have harmful effects which exceed the limits tolerable in the light of current medical knowledge*.

Section 6 AMG empowers the Federal Ministry for Health and Social Security (Federal Ministry) *to specify, restrict or prohibit, by ordinance subject to the approval of the chamber of parliament representing the federal states (Bundesrat), the use of certain substances, preparations made from substances or objects in the*

* The Drug Law does not apply to medical devices.

manufacture of drugs and to forbid the marketing of drugs which have not been manufactured in compliance with these regulations in so far as this is deemed necessary in order to prevent drugs from posing a direct or indirect hazard to human or animal health. The ordinance referred to in sub-section 1 shall be promulgated by the Federal Ministry for Consumer Protection, Nutrition and Agriculture in agreement with the Federal Ministry as far as drugs intended for administration to animals are concerned. In the case of radiopharmaceuticals and drugs in the manufacture of which ionising radiation is used, the ordinance referred to in sub-section 1 shall be promulgated in agreement with the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety.

If a patient experiences any adverse drug reaction with the use of a drug, the patient may report this to a member of the health-care profession. The health-care professional may also have observed the reaction himself. The member of the health-care profession reports the case to the pharmaceutical company or to his professional drug commission or directly to the competent higher federal authority. In some cases, patients also report cases directly to the pharmaceutical company or to the authorities. The competent higher federal authority records the information and evaluates the risk of the medicinal product. Depending on the severity of the reaction, the competent higher federal authority may also communicate the case to the competent higher health or veterinary authority of the federal state (Land) in which the pharmaceutical company is sited and then to the central authority of the federal states for protection of health with regards to the use of medicinal products and medical devices, the drug commissions, the German associations of the pharmaceutical industry, etc., as outlined in the administrative regulation "Allgemeine Verwaltungsvorschrift zur Beobachtung, Sammlung und Auswertung von Arzneimittelrisiken (Stufenplan) nach §63 des Arzneimittelgesetzes.

If the reaction is new and severe, an expedited communication takes place. An assessment of the adverse drug reaction is done and normally the pharmaceutical company, the surveillance authorities and the regulatory authorities decide together which measures should be taken to minimise the risk of the adverse drug reaction¹¹. These measures usually involve amendments to the Summary of Products Characteristics (SmPC) and the Patient Information Leaflet (PIL) and may also involve the labelling of the inner and outer packaging. Thus the information given to health professionals and patients about the medicinal product is adapted to include new knowledge that has been gained about its use with the aim of reducing the risks associated with it. These amendments may include the addition of ADEs to the list of possible adverse drug reactions and the addition of warning statements. The use of the medicinal product may also be restricted to a particular population or certain populations may be excluded from the use of the drug. The competent higher federal authority may also inform the public about drug related risks and envisaged measures. In very serious cases, the product may be withdrawn from the market and the marketing approval revoked.

The obligations of the competent higher Federal Authority (BfArM or PEI) to record and evaluate risks occurring during the administration of drugs and to co-ordinate the measures to be adopted are stated in Section 62 of the drug law. The execution of the tasks of the higher federal authority are detailed in a graduated plan (Stufenplan) in accordance with Section 63 of the Drug Law, which specifies the details of the co-operation to take place between the authorities and the services involved at the various danger levels, as mentioned above, as well as the intervention of the pharmaceutical company and stipulates the various measures to be taken in compliance with the provisions of the law.

Section 25, sub-section 10 of the Drug Law together with sections 5 (prohibition in

respect of unsafe drugs) and section 8 (prohibitions to prevent deception) stipulate the personal responsibility of the pharmaceutical entrepreneur. According to section 25, sub-section 10 of the Drug Law, *the marketing authorisation shall be without prejudice to the pharmaceutical entrepreneur's penal or civil liability*. The pharmaceutical entrepreneur is responsible for the implementation of all measures to be taken to reduce the risks associated with a medicinal product.

Every pharmaceutical entrepreneur (apart from a few exceptions) must appoint a commissioner for the graduated plan (Stufenplanbeauftragter), who is responsible for the collection, evaluation and co-ordination of any necessary measures. He is the central contact person within the pharmaceutical company and also for the regulatory and surveillance authorities¹². The responsibilities of the commissioner for the graduated plan are laid down in section 63a, sub-section 1 of the Drug Law and also in section 14 PharmBetrV. The necessary qualifications of the commissioner for the graduated plan are also laid down in the AMG. Unlike the qualified person according to EU regulation, the commissioner for the graduated plan according to the Drug Law is personally liable for his activities. According to the current law, the pharmaceutical company must notify the competent surveillance authority about who the commissioner for the graduated plan is, including his contact details, and about any related changes.

2.4 Types of Adverse Drug Reactions and Sources for Reports

Adverse Drug Reaction (ADR): This means *“a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function”*¹⁵. A **side effect** also means a response to a medicinal product but is not necessarily unintended. In the daily usage of the German language, adverse drug reactions (unerwünschte Arzneimittelwirkung) and side effect (Nebenwirkung) are used as synonyms; the term side effect is used in the German Drug Law to mean adverse drug reaction¹⁶. In section 4, sub-section 13 of the 12th amendment of the German Drug Law, side effects are defined as *noxious, unintended reactions that occur when a medicinal product is applied in accordance to its intended use*. A reaction, contrary to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected, i.e. judged possible by the reporting or a reviewing health-care professional. An **adverse drug event (ADE)** is defined as *“an undesirable experience occurring following administration of a medicinal product”*¹⁵.

According to the Rules Governing Medicinal Products in the European Union, Volume 9 - Pharmacovigilance, *“a reaction, contrary to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected, i.e. judged possible by the reporting or a reviewing health-care professional. If a reaction is spontaneously reported by a health-care professional, this usually implies a positive judgement from the reporter unless the reporter explicitly gives a negative judgement on the casual relationship”*¹⁵.

Serious Adverse Reaction (SAR): This means *“an adverse reaction which results in death, is life threatening, requires inpatient hospitalisation, or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect. It also includes serious adverse clinical consequences associated with use outside of the terms of the Summary of Products Characteristics (SmPC) (including, for example, prescribed doses higher than those recommended), overdose or abuse”*¹⁵. According to the Rules Governing Medicinal Products in the European Union, Volume 9 - Pharmacovigilance, important adverse

reactions “that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient should also be considered as serious”.

Serious Adverse Event (SAE): This means an adverse event which results in death, is life threatening, requires inpatient hospitalisation, or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect²⁵.

Unexpected Adverse Reaction (UAR): This means “an adverse reaction, the nature, severity or outcome of which is not consistent with the SPC. It also includes class-related reactions which are mentioned in the SPC but which are not specifically described as occurring with this product”¹⁵. For investigational medicinal products, used during a clinical trial, these are reactions “the nature or severity of which is not consistent with the applicable product information (e.g. Investigator’s brochure for an unauthorised investigational product or summary of product characteristics for an authorised product)”²⁵.

A suspected serious UAR is called **Suspected Unexpected Serious Adverse Drug Reaction (SUSAR)**.

Unlisted Adverse Drug Reaction: This means an adverse reaction “which is not specifically included as a suspected adverse effect in the company core safety information (CCSI)*. This includes an adverse reaction whose nature, severity, specificity or outcome is not consistent with the information in the CCSI. It also includes class-related reactions which are mentioned in the CCSI but which are not specifically described as occurring with this product”¹⁵.

Sources for Reports of adverse drug reactions are:

- Spontaneous reports: These are communications to a company, regulatory authority or other organisation that describe a suspected adverse drug reaction in a patient given one or more medicinal products and which do not derive from a study¹⁵.
- Case reports from the word-wide literature: “the marketing authorisation holder is expected to screen world-wide scientific literature and report promptly published suspected serious adverse reactions associated with the use of the active substances(s) of its medicinal products”¹⁵
- Internet, even though, according to the 4th Promulgation of Reporting Obligations, the competent higher federal authority does not expect the MAH to screen the internet regularly for adverse reactions associated with the use of the its medicinal products¹⁶
- Case reports from the competent authorities of other countries¹⁶
- Solicited reports: these are reports derived from “organised data collection systems, which include clinical trials, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or health-care providers, or information gathering on efficacy or patient compliance”³⁶
- Post-Authorisation Studies and Post-Authorisation Safety Studies¹⁶
- Other sources: non-medical sources such as the lay press or other media. According to the note for Guidance on Definitions and Standards for Expedited Reporting (CHMP/ICH/3945/03), “if the MAH becomes aware of a case report from these sources, it should be handled as a spontaneous report. For the

* The CCSI is the safety information contained in the Company Core Data Sheet (CCDS). The CCDS is a document which is prepared by the MAH and which covers material relating to safety, indications, dosing, pharmacology and other information concerning a product (Volume 9 - Pharmacovigilance, Medicinal Products for Human use and Veterinary Medicinal Products)

determination of reportability, the same criteria should be applied as for other reports”³⁶.

2.5 Safety during Research in the Pre-Approval Phase

The development of a medicinal product before marketing authorisation approval can be divided into different stages. After the screening stage, any substance which looks promising undergoes further experiments in which the effectiveness, toxicology and pharmacology of the substance is tested in animals. It is only after certain toxicological experiments have been passed by the substance that it can be investigated in humans and thus enter the clinical trial phase of development. The clinical trials are designed to determine the pharmacological, pharmacokinetic and pharmacodynamic effects of the substance in humans and/or to identify any adverse reactions of the drug. Clinical trials are divided into four phases. The first three phases constitute the clinical development while the fourth phase is conducted after marketing authorisation approval. Short definitions of the four phases are given below¹³:

Phase I:

This involves the studies of pharmacokinetic effects on a few healthy human volunteers or patients (for instance for oncology medicinal products).

Phase II:

This “involves clinical studies on a few hundred volunteer patients to determine the appropriate dose and learn about the activity of the product against the disease. Under certain circumstances, taking into account ethical considerations, type of disease, etc. it may involve comparison with a non-active treatment, called placebo”.

Phase III:

These are trials to test the treatment on several hundred to several thousand voluntary patients, often at many different clinics or hospitals (multi-centre trials), and even in different countries (multi-state trials). These trials usually compare the new treatment with a current one.

Phase IV:

These trials take place after marketing authorisation to gather data on a product authorised for marketing and used in accordance with the approved current medical practice.

Clinical trials included in any marketing authorisation application in the EU are required to be conducted in accordance with Good Clinical Practice (GCP), found in the Directive 2001/83/EC Annex I, as amended by Directive 2003/63/EC.

Suspected cases of adverse drug reactions must be recorded. These records must be presented to the competent higher federal authority within the given deadline or immediately, upon request. All available documents for the evaluation of suspected cases and a scientific assessment must be also be presented to the competent higher federal authority¹⁴. The obligations for the collection, recording and notification of adverse drug events are detailed in the Good Clinical Practice Regulation (GCP-V) of 9 August 2004. The legal basis for this regulation is found under section 42, subsection 3 of the 12th amendment of the German Drug Law. Once a marketing authorisation has been applied, the obligations of the applicant for the documentation and reporting of ADRs pursuant to section 63b of the 12th amendment of the German Drug Law also apply.

2.6 Safety during Research in the Post-Approval Phase

Part of the process of evaluating drug safety needs to occur in the post-approval phase, as clinical trials during the pre-approval phase have limitations in defining the risks and benefits of drugs because of the limited number of patients, limited types of patient groups and limited administration regimens or indications. If it would not be possible to extend part of the process of evaluating drug safety to the post-authorisation phase, important innovations would be lost in an unduly restrictive regulatory net^{8, 62}.

Post-Authorisation Study: According to the definition for post-authorisation study found in the rules for Governing Medicinal Products in the European Union, Volume 9 - Pharmacovigilance, Part I/3, Terminology¹⁵, a post authorisation study is *“any study conducted within the conditions of the approved Summary of Product Characteristics (SPC) or under normal conditions of use. A post-authorisation study may sometimes also fall within the definition of a post-authorisation safety study (PASS). In relation to ADR reporting and PSUR requirements, reference to a post-authorisation safety study means any post-authorisation study of which the marketing authorisation holder is aware.”* A phase IV trial is a post-authorisation study (compare point 2.5) and may also be a post-authorisation safety study (see below).

Post-authorisation safety study: According to the rules for Governing Medicinal Products in the European Union, Volume 9 - Pharmacovigilance, Part I/3, Terminology, a post-authorisation safety study *“means a pharmacoepidemiological study, or a clinical trial carried out in accordance with the terms of marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product”*. It goes on to say that any study where the number of patients to be included will add significantly to the existing safety data for the product is also considered a PASS^{15, 16}.

Post-authorisation studies and post-authorisation safety studies fall under the clinical trials regulations found under sections 40 to 42a of the 12th amendment of the German Drug Law and therefore also under obligations for the documentation and reporting of ADRs during clinical trials. In addition to this, the regulations found under section 63b of the 12th amendment of the German Drug Law also apply to Post-authorisation studies and post-authorisation safety studies as the medicinal products used for the study are used in accordance with the terms of marketing authorisation.

Pharmacoepidemiological study: The main purpose of drug epidemiology, or pharmacoepidemiology, is to determine the impact of medicinal products on the health of the population⁶⁰. It is the science of studying drug effects in populations. “It is primarily focussed on measuring safety in the post-marketing phase. Pharmacoepidemiological studies are **observational** (whereas clinical trials are experimental or interventional) - they attempt to measure effects under real-life conditions. Larger populations can be studied than in clinical trials and the findings are likely to be generally applicable. However, without randomisation, attribution of causation is more difficult. Observational studies provide evidence of **association** (or no association) and a judgement then has to be made on causation taking into account all the available information. Pharmacoepidemiological studies are frequently conducted on data collected for other purposes, in particular, routine general practice data⁶¹.”

Non-interventional trials: The purpose of non-interventional trials is to gain knowledge about medicinal products, which have obtained a marketing authorisation approval⁵⁹. Complementary to clinical studies, they are adequate tools that can be used for increasing drug safety⁵⁸. The effects of the medicinal product are observed

under routine conditions using the normal finished medicinal product, which is available on the market⁵⁹. In Directive 2001/20/EC, a non-interventional trial is defined as „*a study where the medicinal product(s) is prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data*“. This definition has been taken over for the most part in section 4, subsection 23 of the 12th amendment of the German Drug Law, which also states that non-interventional trials are no clinical trials. Non-interventional trials do not fall under the regulations for clinical trials found under sections 40 to 42a of the 12th amendment of the German Drug Law. They are also excluded from the clinical trials directive 2001/20/EC¹⁶. Obligations to record and report adverse drug reactions are regulated pursuant to section 63b of the 12th amendment of the German Drug Law.

3. ISSUES UNDER EXAMINATION

Up until 1961, there was no drug law in Germany. However, some areas of pharmaceutical legislation were regulated in various laws and regulations. The first draft for a law governing the dealings with medicinal products was issued in 1952 and finally came into force on 1 August 1961 (Gesetz über den Verkehr mit Arzneimitteln) after long deliberations and several revisions. This law was amended several times after that, especially by the amendment of 23 June 1964, to meet the increased requirements for drug safety. With the Regulation for the Assessment of Medicinal Products (Richtlinie über die Prüfung von Arzneimitteln) of 1971, a higher standard was set for the documents, which had to be submitted for the registration of a medicinal product. This was to enable the Ministry of Health (Bundesgesundheitsamt, BGA) to exert more control for with the aim of the prevention of drug hazards. The second Drug Law (Gesetz zur Neuordnung des Arzneimittelrechts), which came into force on 1 January 1978, was not a complement to the AMG of 1961 but a new law with regard to structure and contents. The objective of the new law was a further optimisation of drug safety. It enables stricter controlling of manufacturers, an intensive assessment of the medicinal product before approval and the continuous surveillance after approval²¹. Section 1 of the Drug Law states that the purpose of the present law is *to ensure, in the interest of furnishing both human beings and animals with a proper supply of drugs, safety in respect of the trade in drugs, ensuring in particular the quality and safety of drugs in accordance with the following provisions*. The second drug law has been amended several times since 1978 to adapt to international standards²¹ and to accommodate the advancements of the recent years. The accelerated progress has led to 9 amendments within 15 years only i.e. between 19 April 1990 (4th amendment) and 6 August 2004 (12th amendment) and the 14th amendment is expected to come into force in October 2005.

There have been several amendments to the European pharmaceutical legislation in the past few years. Directive 65/65/EEC is the basis of the pharmaceutical legislation of the European union. It includes relevant definitions (medicinal product, proprietary medicinal product, officinal and magisterial formula, etc.), and states the registration for all proprietary medicinal products¹⁷. Since 1965 this Directive was amended several times which resulted in a wide system of regulations and directives, which were no more consistent in all points. Due to this, the EU-Commission started a two-

* quoted from the 12th amendment of the German Drug Law

staged process end of the last decade to amend the complete pharmaceutical legislation. The first stage consisted of merging a number of directives into one consistent directive, EU directive 2001/83/EG and in the revision of Regulation 2309/93¹⁸. During the second stage, amendments were made to the contents of the most important provisions. This finally led to the publication of Regulation (EC) No 726/2004, replacing Regulation (EC) 2309/93, which lays down regulations governing authorisation and supervision of medicinal products through the centralised procedure and for organisational changes of the EMEA and the directive 2004/27/EC (relating to medicinal products for human use), amending Directive 2001/83/EC, Directive 2004/28/EC (relating to veterinary medicinal products), amending Directive 2001/82/EC and 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. These directives apply to medicinal products whose marketing authorisations have been granted through the Mutual Recognition Procedure (MRP).

All regulations issued by the EU are binding and directly applicable in all member states. They do not require any transposition by the national authorities¹⁹. A directive is legally binding to all member states to which it is addressed but must be transposed into the legal order of the member states within 18 months in order to take effect.

The Directive 2001/83/EG and Directive 2001/82/EG were transposed into the national legal order in Germany in the 12th amendment of the German Drug Law. Furthermore, Directive 2001/20/EG on the approximation of laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use and Directive 2002/98/EG, setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending directive 2001/83/EG were also transposed into German legal order in the 12th amendment of the German Drug Law. In addition, the 12th amendment of the German Drug Law also contains changes, which were made because of experiences made during the execution of the 11th amendment of the German Drug Law²⁰.

In February 2005, a draft for the 14th amendment of the German Drug Law was issued to transpose Directive 2004/27/EC and directive 2004/28/EC into national law.

The purpose of this thesis is to describe the changes that have been introduced into the national German Drug Law in the field of pharmacovigilance as a result of the transposition of EU regulation and for other reasons such as the experience made with the old law. The main focus is on medicinal products for human use but veterinary medicinal products shall also be mentioned for the sake of completeness.

4. THE 12TH AMENDMENT OF THE GERMAN DRUG LAW

4.1 EU Directive 2001/83/EC and 2001/82/EC

As already described briefly in section 3 of this thesis, Directive 2001/83/EG of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use consists of a number of directives which were merged into one consistent directive. It applies to industrially produced medicinal products for human use intended to be placed on the market in member states. It presents an important step towards achievement of the objective of the free movement of medicinal products²⁴. The directive lays down rules governing marketing approval procedures through the Mutual Recognition Procedure, the

manufacture and importation of medicinal products, the labelling and package leaflet of MRP products, the classification of these products, the wholesale distribution of medicinal products, advertising, pharmacovigilance, special provisions on medicinal products derived from human blood and plasma, provisions on communication between regulatory authorities in the member states, the MAH and the EMEA, etc.. The provisions concerning pharmacovigilance are found in Article 101 to 108. They were introduced into the EU legislation with Directive 2000/38/EC, which amended Directive 75/319/EC. The deadline for the transposition of the provisions of Directive 2000/38/EC into national legislation was 5 December 2001²¹. However, the Federal Government of Germany was not willing to transpose this law into national law because of various points of disagreement and brought the action before the Court of Justice of the European Communities on 30 August 2000 where the Federal Republic of Germany claimed that the court should annul the Directive²². The outcome was negative and the Federal Government of Germany then brought the case before the European Court of Justice but withdrew the case after the directive was integrated into the Directive 2001/83/EC²⁰. Finally, Directive 2001/83/EC was transposed into national legislation with the 12th amendment of the German Drug Law. Directive 2001/82/EC is the equivalent European legislation for veterinary medicinal products and was also transposed into national with the 12th amendment of the German Drug Law.

4.2 EU Directive 2001/20/EG

The full title of the Directive is "Directive of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use". It establishes specific provisions regarding the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products as defined in Article 1 of Directive 65/65/EEC, in particular relating to the implementation of good clinical practice. It does not apply to non-interventional trials²⁵. The main aim of the Clinical Trials Directive 2001/20/EC is to simplify and harmonise the administrative provisions governing clinical trials by establishing a clear, transparent procedure and creating conditions conducive to the effective co-ordination of such clinical trials in the European Community by the authorities concerned²³.

The Directive addresses a number of key areas in the conduct of clinical trials.

Among others:

- It requires member states to establish ethics committees for the purpose of implementation of clinical trials. It also defines the obligations of the ethics committees, including the procedures and timeframes for issue of an opinion concerning a clinical trial.
- It requires all member states to comply with Good Clinical Practice (GCP) in the conduct of clinical trials.
- It contains provisions for the protection of clinical trial subjects, including children and incapacitated adults not able to give informed legal consent.
- It contains provisions for the commencement and conduct of a clinical trial, for the exchange of information, the manufacture of investigational medicinal products (IMPs) and labelling of IMPs.
- It Introduces responsibilities for sponsors and investigators in adverse drug reaction (ADR)/adverse drug event (ADE) reporting.

The provisions on reporting of adverse event and reaction are found in Articles 16 to 18.

Agreement on this Directive was reached in February 2001 and the final version was

published in the "Official Journal of the European Communities" on 1 May 2001. Member States had time until 1 May 2003 to prepare national provisions for complying with the Directive and were to adopt those provisions by 1 May 2004²³. This directive was transposed into German legal order in the 12th amendment of the German Drug Law.

4.3 Changes in the field of pharmacovigilance in the 12th amendment of the German Drug Law

4.3.1 New Definitions (Section 4, sub-section 13 AMG)

New definitions have been added to the list of definitions found in section 4, sub-section 13 of the German Drug Law.

Side effects: as mentioned under point 2.4, the terms side effect ("Nebenwirkung") and adverse drug reaction ("unerwünschte Arzneimittelreaktionen") are used as synonyms. According to the former definition, ***side effects** are those undesired concomitant effects, which occur when a drug is administered in keeping with its intended purpose.* The definition has now been changed to read: ***side effects** are those noxious unintended reactions, which occur when a drug is administered in keeping with its intended purpose.* Directive 2001/83/EC states that "***an adverse reaction** is a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function*". The new definition used in the AMG therefore comes closer to the definition used in the directive. It also comes closer to the definition used by the World Health Organisation, WHO "***an adverse reaction** is a response to a medicine which is noxious and unintended and which occurs at doses normally used in man*"⁹. Even though it is not as specific as the EU definition, it is much more precise than the old one. The new definition in the AMG now clearly states that an adverse drug reaction is a noxious unintended reaction and not just an unintended reaction. It is also of importance that an adverse drug reaction is a reaction or a response of a patient to a drug, in which individual factors may play an important role⁹. It must however be noted that this definition for ADRs is not applicable to ADRs during clinical trials because the intended purpose of an investigational medicinal product is not yet clearly defined during most studies³⁹ but a more appropriate definition for ADRs during clinical studies is included in the GCP-V (Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen), which shall be discussed under point 4.3.3.

For the first time, a definition for "serious" and "unexpected" ADRs has been introduced into the AMG²⁰: ***Serious adverse reactions** are adverse reactions which result in death or are life-threatening, require inpatient hospitalisation or prolongation of existing hospitalisation, result in persistent or severe disability, invalidity, congenital anomalies or birth defects; for veterinary medicinal products, those adverse reactions are also serious, which result in permanent or prolonged symptoms.* This definition is similar to the definition that was used for medicinal for human use in the 3rd Promulgation for reporting obligations of 15 May 1996 (3. Bekanntmachung zur Anzeige von Nebenwirkungen, Wechselwirkungen mit anderen Mitteln und Arzneimittelmisbrauch nach §29 Abs. 1 Satz 2 bis 8 AMG), but now includes congenital anomalies or birth defects as a criteria for a serious ADR. It is now in line with the definitions used for serious ADRs for medicinal products for human use and veterinary medicinal products in the Rules Governing Medicinal Products in the European Union, Volume 9 - Pharmacovigilance.

The 4th Promulgation for Reporting Obligations, which amends the 3rd notification due to the changes which have been introduced in the 12th amendment of the German Drug Law, explains that 'life-threatening' refers to an ADR which presents a risk of death at the time of occurrence and not one, which could hypothetically lead to death if it would have occurred with greater severity or would have led to complications. The gravity of an ADR is therefore defined according to the consequence of the reaction¹⁶. The 4th Promulgation for Reporting Obligations also refers to the Rules Governing Medicinal Products in the European Union, Volume 9 - Pharmacovigilance, which recommends that medically significant ADRs be classified as serious as well. These are those that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the patient^{15,16}. It goes on to say that ADRs are also medically significant if they require intervention/treatment to prevent a condition, which would be equivalent to the criteria used for the definition of a serious ADR¹⁶.

Unexpected adverse reactions are *adverse reactions, the nature, severity or outcome of which is not consistent with the package leaflet of the medicinal product*. This definition is also similar to the definitions commonly used internationally. However, according to the definition in the German Drug Law, the package leaflet is the reference document for unexpected drug reactions whereas directive 2001/83/EC and the Rules Governing Medicinal Products in the European Union, Volume 9 - Pharmacovigilance define the SmPC as being the reference document. It would have been more expedient to refer to the SmPC as reference document as this is the basis document, according to EU legislation, which is used for the creation of the package leaflet³⁹ and it often contains less information than the SmPC. In addition, the PIL is not yet harmonised in the Member States (this will be the case as from 1 November 2005 for new applications and repeat-use applications), which means that an unexpected ADRs in Germany might not be an unexpected ADR in other Member States. This would lead to unnecessary complications. It is probably because of these reasons that the 4th Promulgation for Reporting Obligations (4. Bekanntmachung zur Anzeige von Nebenwirkungen, Wechselwirkungen mit anderen Mitteln und Arzneimittelmisbrauch nach §63 Abs. 1 bis 8 AMG), states that the SmPC is to be used complementary to the package leaflet as reference document for classifying an adverse reaction as being unexpected.

Furthermore, this definition is not applicable to unexpected ADRs during pre-approval clinical trials because the investigational medicinal product does not have a PIL³⁹. Again, the GCP-V includes a definition for unexpected ADRs during clinical studies.

A further new definition, which has been introduced into the 12th amendment of the German Drug Law, is the definition for **drug interactions**. It states that sentences 1 to 3 of section 4, sub-section 13 (i.e. the definitions for ADRs, serious ADRs and unexpected ADRs) *also apply to adverse drug reactions which occur due to drug interactions*. With this definition, drug interactions are categorised as a special form of drug hazard⁵⁶. They have been added to the list of drug hazards in the new graduated plan of 9 February 2005 (compare point 4.3.5) and must also be reported according to section 63b of the 12th amendment of the German Drug Law (see point 4.3.6). The definition for drug interactions is not deducible from European law²⁰.

4.3.2 Costs (Section 33 AMG)

According to the 12th amendment of the German Drug Law, the higher competent authority can now levy charges *for activities carried out in the course of collecting and assessing risks associated with medicinal products*. Before the 12th amendment of the German Drug Law came into force, such activities that were conducted by the higher federal competent authorities in Germany were free of charge. There is no legal basis for these fees in the Directives 2001/83/EC or 2001/82/EC. According to the explanatory text for the 12th amendment of the German Drug Law, the justification for this is that the activities related to pharmacovigilance are special administration services which should not only be paid by public funds alone but are also imputable to the pharmaceutical companies which market the medicinal products²⁹.

The pharmaceutical industry, on the other hand, feels that these charges are contra productive for drug safety and should only be charged when the authorities are forced to impose measures on a company in relation to drug safety. Gaining knowledge about the risks of a medicinal product is essential for devising measures for their prevention or reduction and the various parties involved with this (government authorities, pharmaceutical companies, medical professionals, drug commissions and patients) have been doing their part free of charge up till now³⁹. However, it can be seen positively, that in opposition to the original plan, now only the assessment of PSURs is levied with charges. Fees for every submitted report would have resulted in a very complicated issue with a high financial burden for the pharmaceutical industry. Germany would have also further lost its attractiveness as a site for clinical studies because of the high financial burden of reporting numerous cases not only during the trial but also at its end (usually dozens to hundreds!). In addition, this would have resulted in very high administrative efforts and the need for more staff on the side of the authorities, considering the number of invoices, which would have had to be issued and the number of queries and even legal proceedings in connection with fee reduction³⁹.

The first amendment of the regulation for fees due for activities carried out by the competent higher federal authority was promulgated in the Bundesgesetzblatt of 28 December 2004 (BGBl. I S. 3719) and came into force on 29 December 2004. Table 1 shows the Fees due for the assessment of PSURs:

Table 1: Fees due for activities carried out by the competent higher federal authority in connection with drug safety (assessment of PSURs), as published in the Bundesgesetzblatt

e) Nach der Gebühren-Ziffer 21 werden die folgenden Gebühren-Ziffern eingefügt:

Gebühren-Ziffer	Gebührenpflichtige Amtshandlung	Gebühr in Euro
„22	Bewertung eines Berichts über die Unbedenklichkeit des Arzneimittels nach § 29 Abs. 1 Satz 4 bis 6 oder § 63b Abs. 5 AMG	
22.1	Bewertung eines Berichts über die Unbedenklichkeit für Arzneimittel im gegenseitigen Anerkennungsverfahren mit Deutschland als Referenzmitgliedstaat (RMS) innerhalb von zehn Jahren nach erstmaliger Zulassung des Arzneistoffes in Deutschland	6 360
22.2	Bewertung eines Berichts über die Unbedenklichkeit für Arzneimittel im gegenseitigen Anerkennungsverfahren mit Deutschland als Referenzmitgliedstaat (RMS) später als zehn Jahre nach erstmaliger Zulassung des Arzneistoffes oder im gegenseitigen Anerkennungsverfahren mit Deutschland als betroffenem Mitgliedstaat (CMS) innerhalb von zehn Jahren nach erstmaliger Zulassung des Arzneistoffes oder im nationalen Zulassungsverfahren innerhalb von zehn Jahren nach erstmaliger Zulassung des Arzneistoffes	1 635
22.3	Bewertung eines Berichts über die Unbedenklichkeit für Arzneimittel im gegenseitigen Anerkennungsverfahren mit Deutschland als betroffenem Mitgliedstaat (CMS) später als zehn Jahre nach erstmaliger Zulassung oder im nationalen Zulassungsverfahren später als zehn Jahre nach erstmaliger Zulassung	525
22.4	Werden gleichzeitig identische periodische Berichte nach Ziffer 22.1, 22.2 oder 22.3 vorgelegt und bewertet, entsteht die Gebühr nach Ziffer 22.1, 22.2 oder 22.3 nur ein Mal. Für jeden weiteren identischen periodischen Bericht reduziert sich die Gebühr auf	200“.

f) Die bisherigen Gebühren-Ziffern 22, 22.1 bis 22.7 werden Gebühren-Ziffern 23, 23.1 bis 23.7.

As shown in the table above, 6 360 € are due for the assessment of a PSUR for a medicinal product with Germany as RMS within 10 years after the first marketing authorisation approval **in Germany**. The addition of the phrase “in Germany” clarifies that this regulation does not apply to every single MAH but applies to all concerned marketing authorisations in general. Therefore, this fee does also not apply to a PSUR for a generic of the medicinal product. This is fair because the risks of a medicinal product are normally known to a large extent after 10 years of marketing and new knowledge, which may affect the benefit-risk balance of the active substance, is rare, which also means less work for the competent higher federal authority in the assessment of such PSURs⁶³.

1 635 € are to be paid for the assessment of a PSUR for a MRP product for which Germany is the RMS after 10 years of first approval or for a MRP product for which Germany is CMS within 10 years after first approval or for a nationally approved product within 10 years after first approval.

525 € are to be paid for the assessment of a PSUR for a MRP product for which Germany is the CMS after 10 years of first approval or for nationally approved product after 10 years of the first marketing approval.

When several identical PSURs are submitted and assessed at the same time, the

normal fee is due only for the first PSUR while the fees for the following PSURs is reduced to 200 €.

The fees for the assessment of PSURs are generally speaking quite high. A fee of 6360 € suggests a very high work load for the competent higher federal authorities, however, the charges for an external consultant who prepares such a PSUR is often below this price and can therefore be seen critically⁶³. The high costs for PSURs when Germany is RMS during an MRP may also lead to pharmaceutical companies, especially smaller ones, avoiding using Germany as RMS, which may affect the competitiveness of the German competent higher federal authorities negatively.

Even the lowest fee of 525 € can be seen critically for medicinal products which have been on the market for more than 10 years because the risks of a medicinal product are normally known to a large extent and new knowledge on the safety of the drug is rare at this point in time. Therefore the workload for the authorities is also low. In addition, it still has to be clarified whether the reduction of fees also applies to identical PSURs that are submitted by several pharmaceutical companies at the same time and how 'identical' is defined in this context⁶³.

4.3.3 Reporting of adverse drug reactions during clinical trials (Section 42, subsection 3 AMG)

The reporting of adverse drug reactions to the higher competent federal authority during clinical trials was formerly regulated in section 29 of the German Drug Law. Further details were found in the 3rd Promulgation for Reporting Obligations pursuant to section 29, subsection 1, sentence 2 to 8 AMG of 15th May 1996 (3. Bekanntmachung zur Anzeige von Nebenwirkungen, Wechselwirkungen mit anderen Mitteln und Arzneimittelmisbrauch nach §29 Abs. 1 Satz 2 bis 8 AMG) while the notification of adverse drug events to the ethics committee was formerly regulated in section 40, subsection 1 number 8 of the German Drug Law.

One of the major changes introduced to the 12th amendment of the German Drug Law was the revision of the regulations governing clinical studies and adaptation to the contents of the GCP Directive 2001/20/EC. For the first time in Germany, a separate regulation has been issued with detailed regulations for the conduct of clinical trials. The legal basis for this regulation is found in the amended sections 12 and 42 of the German Drug Law. Section 42, subsection 3 empowers the Federal Ministry to issue regulations by ordinance subject to the approval of the parliament (Bundesrat) to guarantee the orderly conduct of clinical trials and the attainment of documents which are in accordance to the state of the art. Section 42, subsection 3 number 1 mentions the documentation in relation to ADRs during clinical studies. Section 12, subsection 1b, number 2 empowers the Federal Ministry, in agreement with the Federal Ministry for Economics and Labour by ordinance subject to the approval of the Bundesrat, to regulate the labelling of medicinal products which are used for clinical studies.

This separate regulation, which is called "Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen (GCP-Verordnung - GCP-V)" of 9 August 2004, came into force on 14 August 2004 and also contains detailed regulations concerning the obligations of the investigator, the sponsor and the competent higher federal authority to report adverse drug reactions which have occurred during a clinical trial. The GCP-V applies to all clinical trials on medicinal products for human use. Only non-interventional trials are excluded²⁶. The details of the reporting liabilities will not be described in this thesis as this would go beyond its scope. However, the main

changes in the reporting liabilities are described briefly below (see copy of the German GCP Regulation in the annex for reference).

Pursuant to the old AMG, the investigator and the sponsor of a clinical study were obliged to *inform the competent higher federal authority immediately, or at the latest within 15 days of it coming to his knowledge, of any case of suspected serious adverse drug reaction or interactions with other products which have become known to him, as well as frequent abuse or individual cases of substantial abuse, if this can directly jeopardise human or animal health.* He was also to keep a record of *all suspicious cases other than serious side effects* or interactions with other substances of which a member of a health profession informed him. In so far as no condition was imposed on the contrary, he was to then transmit these records to the competent higher authority upon request or at regular intervals.

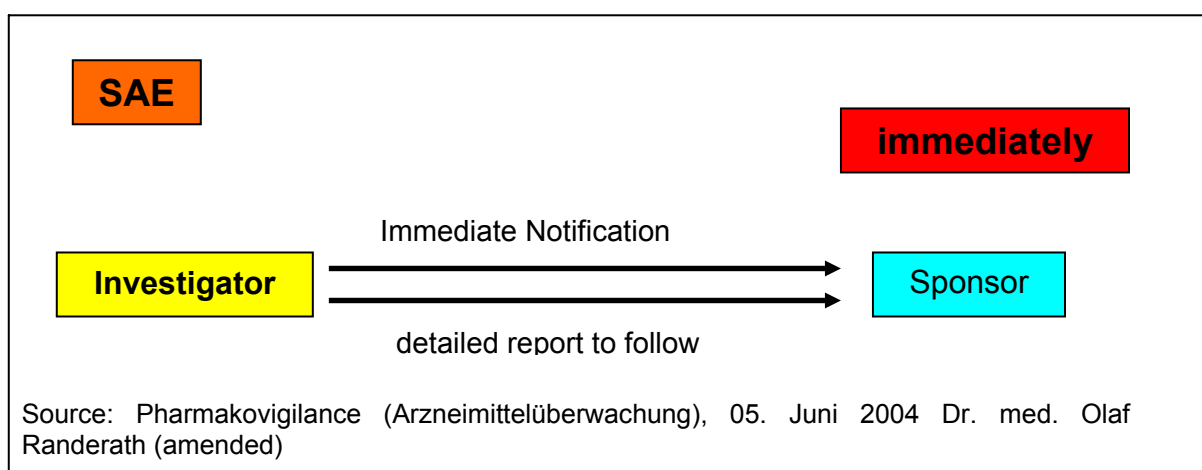
The reporting obligations of the investigator, the sponsor and the competent higher federal authority are listed separately in the GCP-V:

Investigator:

Generally, all health-care professionals in Germany are obliged by their professional statutory orders (Berufsordnung) to report serious adverse drug reactions to their professional drug commissions. Because of this, sponsors formerly had to regulate the reporting of adverse events occurring in clinical trials on a contractual basis with every investigator. With the new GCP-V, the reporting obligations for investigators to the sponsor are now defined for the first time in Germany by law.

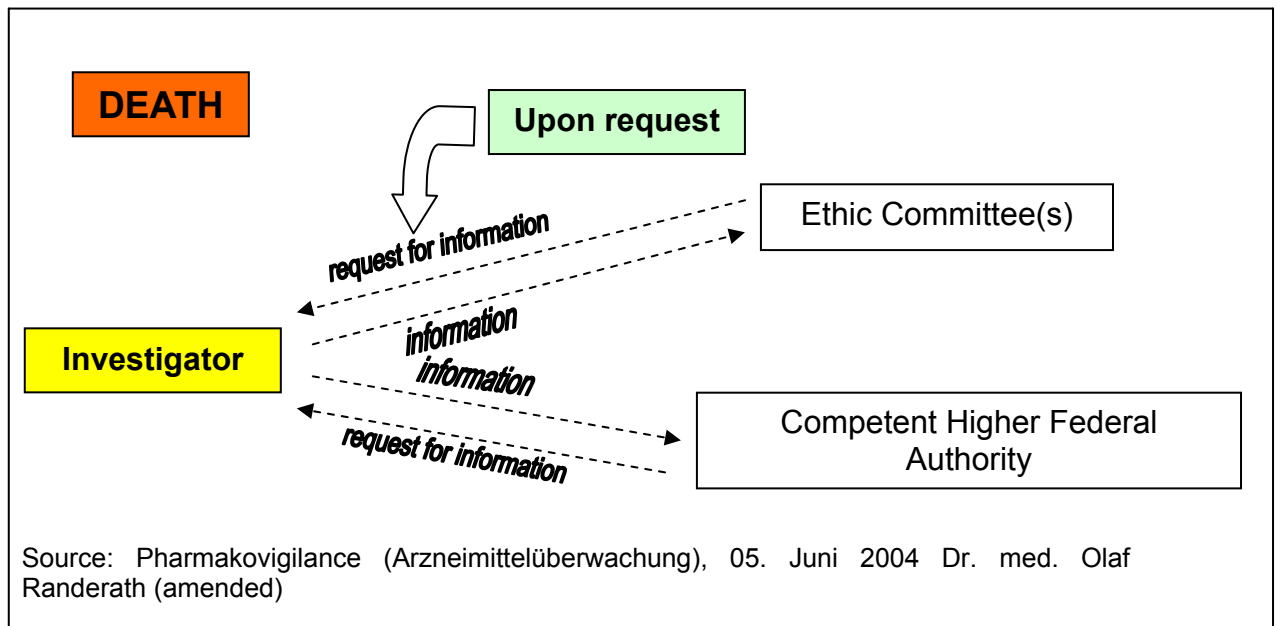
According to the GCP-V, the obligation of the investigator is now to inform the sponsor and no more the competent higher federal authority immediately about adverse and serious adverse drug events and not just adverse drug reactions (see point 2.4 for definitions), except for those that have been exempted from immediate reporting in the study protocol. The investigator must later submit a detailed report about the adverse drug event to the sponsor. Thereby the new law ensures that the sponsor receives as much information about the safety of the investigational medicinal product as possible.

Diagram 1: The Investigator's Reporting Obligations for SAEs



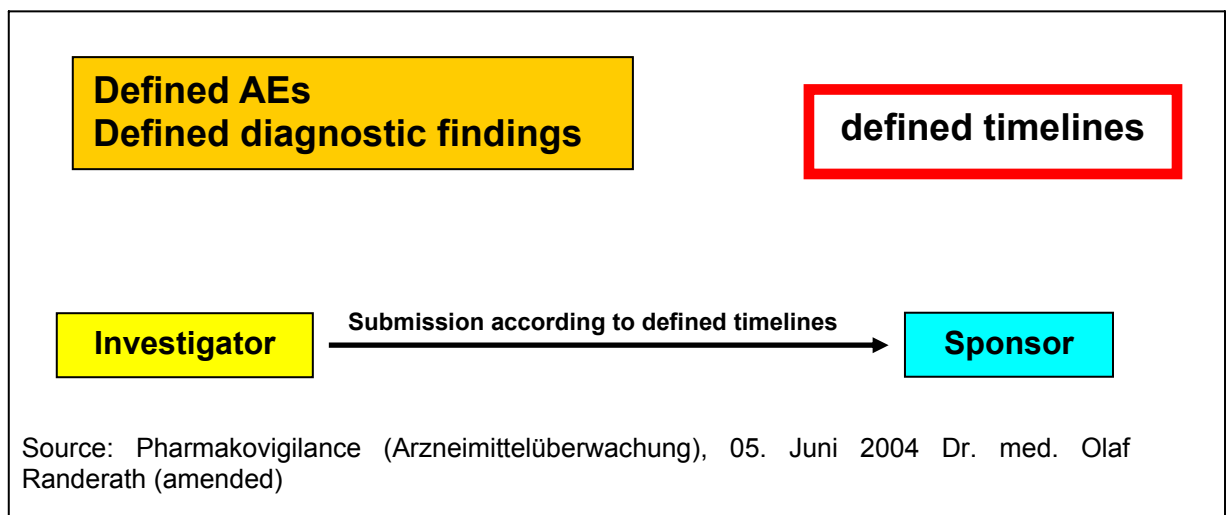
In the case of death, he must also provide all necessary information for the assessment of the case to the ethic commission(s), the competent higher federal authority as well as the sponsor.

Diagram 2: The Investigator's Reporting Obligations in the case of death



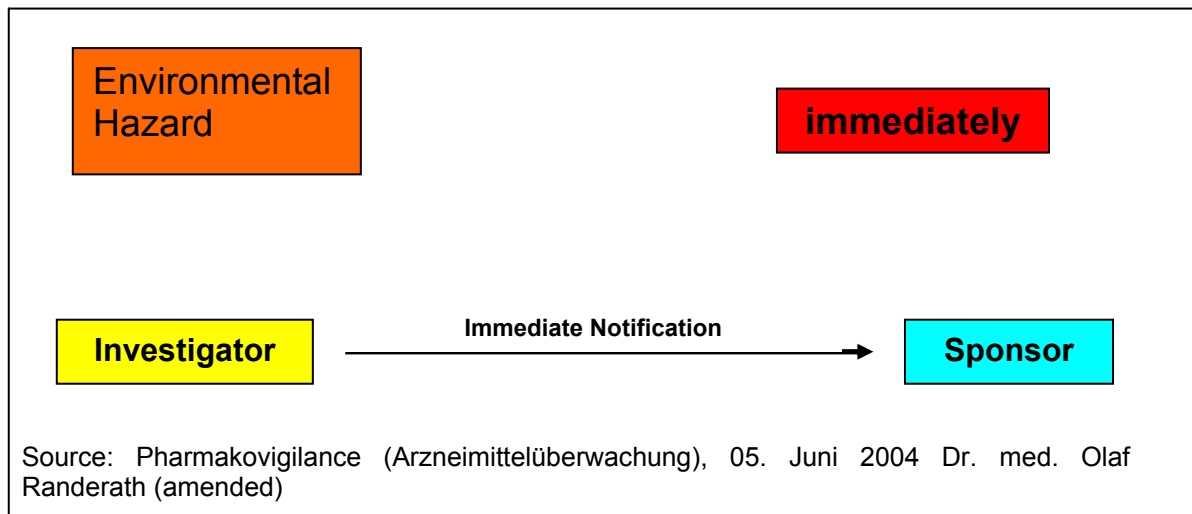
The investigator must report ADEs and diagnostic findings, which are listed in the trial as being crucial to the sponsor within the deadlines defined in the trial protocol.

Diagram 3: The Investigator's Reporting Obligations for defined cases



Observations, which are harmful for the environment and are additional to those already considered in the risk assessment of clinical trials with medicinal products containing genetically manipulated organisms, must be notified to the sponsor by the investigator immediately.

Diagram 4: The Investigator's Reporting Obligations for environmental hazards



Sponsor:

The reporting obligations of the sponsor differ according to the type of adverse drug reactions. The types stated in the GCP-V are:

- Adverse drug events
- Suspected unexpected serious adverse reactions
- Suspected unexpected serious adverse drug reactions that are fatal or life-threatening and
- Harmful effects of genetically manipulated organisms on the health of persons who are not involved in the clinical study and on the environment.

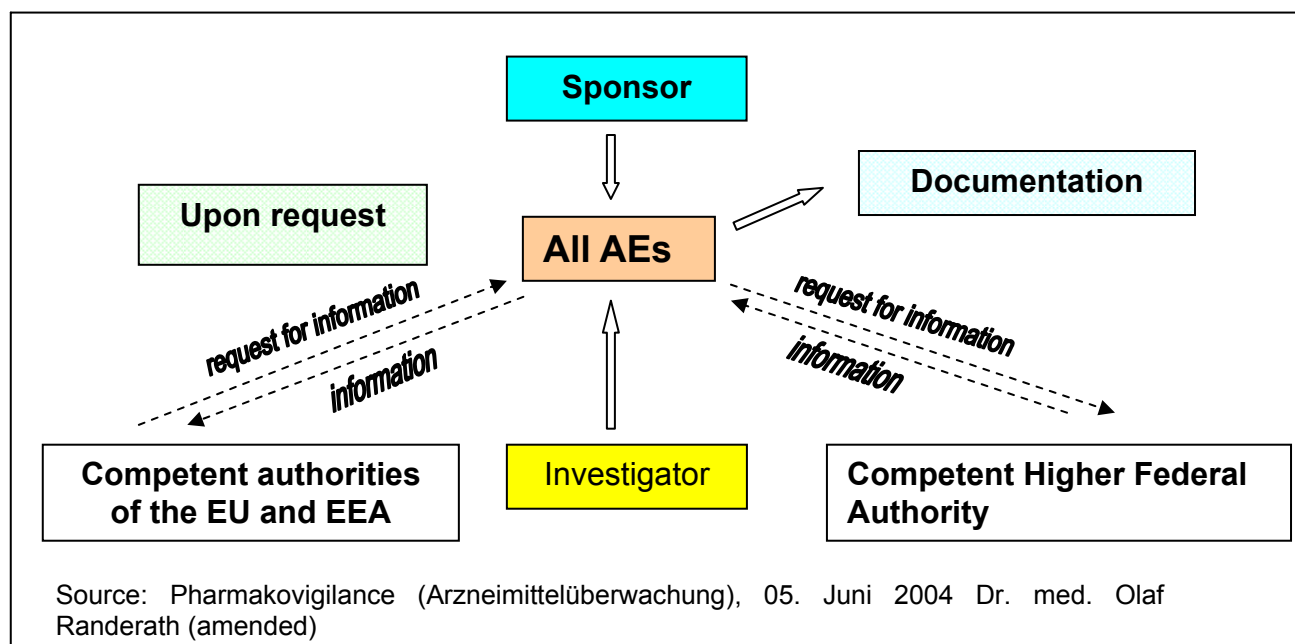
Further more, it differentiates between circumstances that lead to a new assessment of the benefit/risk ratio of the product. These may be:

- Expected serious adverse drug reactions with unexpected outcome
- An increase in expected serious adverse drug reactions with clinical relevance
- Suspected unexpected serious adverse drug reactions that occurred after the affected person had ended the clinical trial and
- Events which are related to the conduct of the study or to the development of the investigational medicinal product and which may potentially affect the safety of the affected persons

(Please see annex for further details).

The sponsor must keep detailed record of all *adverse drug events*, which are reported to him by the investigator. They are to be submitted to the competent higher federal authority and to the competent authorities of the other countries of the EU and the EEA, in which the clinical study is conducted only upon request.

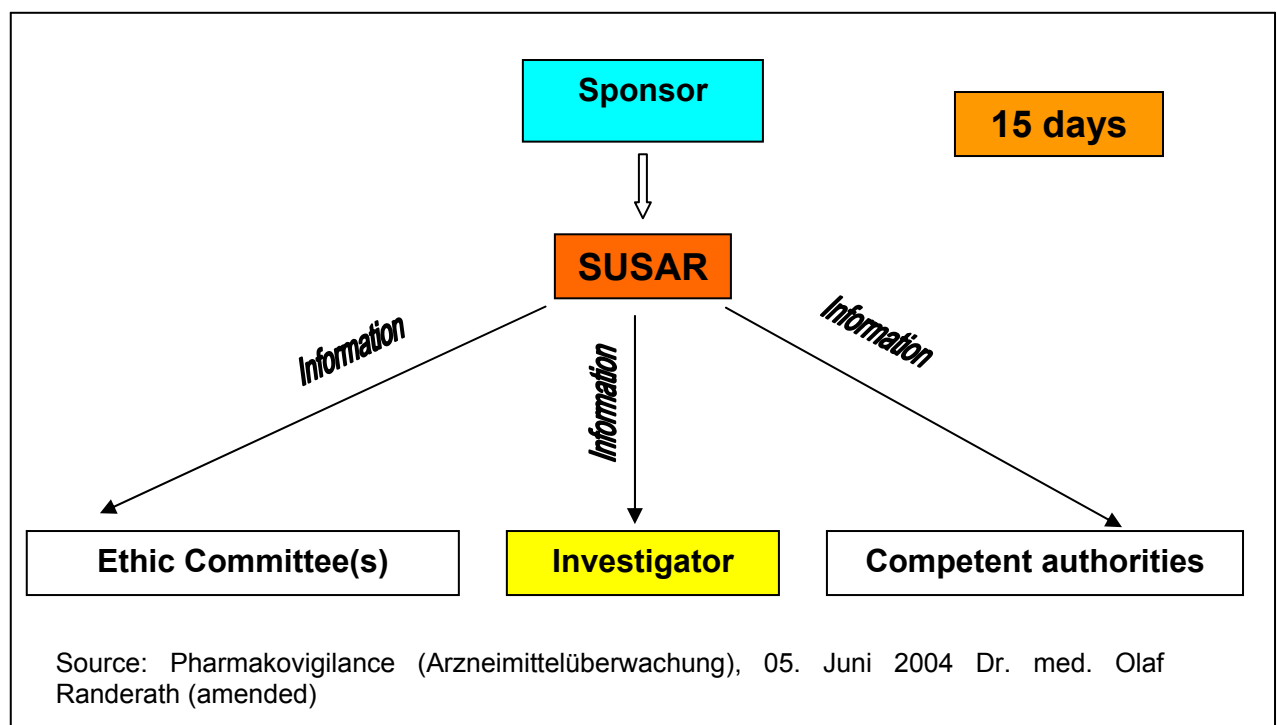
Diagram 5: The Sponsor's Reporting Obligations for ADEs



However, events which are related to the conduct of the study or to the development of the trial product and that may potentially affect the safety of the affected persons and which lead to a new assessment of the benefit/risk ratio of the product, must be reported to the competent ethic committee, to the competent higher federal authority and to the affected competent authorities of the other countries of the EU and the EEA immediately, or at the latest within 15 days of it coming to the sponsor's knowledge.

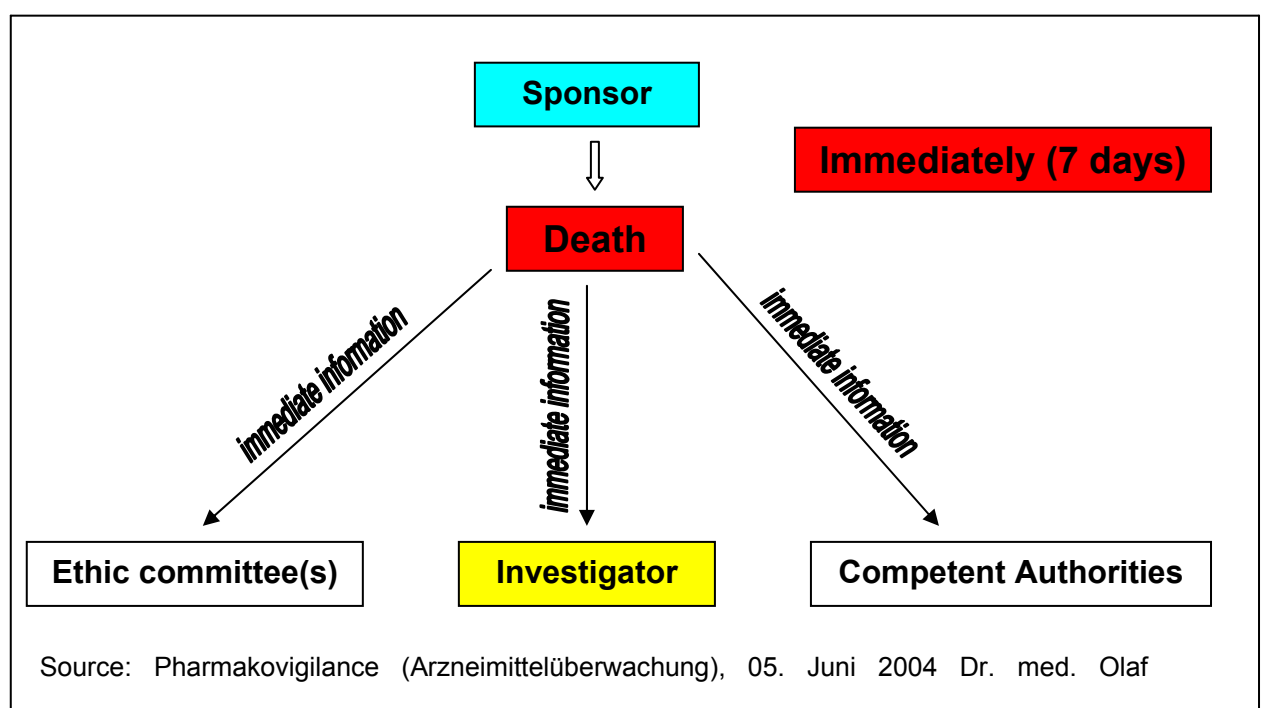
The sponsor must also report all suspected unexpected serious adverse drug reactions (SUSARs) immediately, or at the latest within 15 days of it coming to his knowledge to the competent ethic committee and to the competent higher federal authority and to the competent authorities of the other countries of the EU and the EEA in which the clinical trial is being conducted. The new law clearly states that these reports must be sent not only to the competent ethic committee and to the competent higher federal authority but also to the competent authorities of the other member states of the EU and the EEA in whose territory the clinical trial is being conducted. An exception to this is given for harmful effects of genetically manipulated organisms on the health of persons who are not involved in the clinical study and on the environment. These must be reported immediately to the competent higher federal authority only. This regulation enhances the flow of information, concerning any suspected unexpected serious adverse drug reaction that has occurred due to the use of the investigational medicinal product, between all concerned parties and hence enhances the safety of the product.

Diagram 6: The Sponsor's Reporting Obligations for SUSARs



Formerly, there was no difference in the German Drug Law for the reporting deadline for suspected serious unexpected adverse reactions that are fatal or life-threatening and other SUSARs. Now, the sponsor of such a case must report SUSARs that are fatal or life threatening immediately but no later than 7 days after its coming to his knowledge.

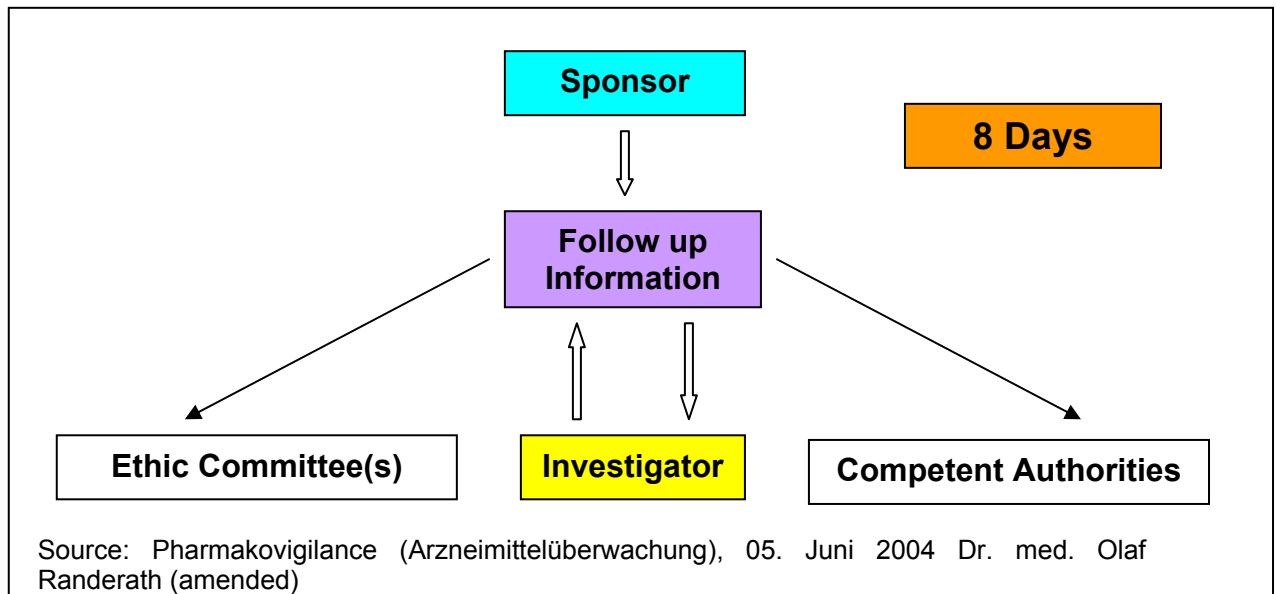
Diagram 7: The Sponsor's Reporting Obligations for cases that are life threatening or have lead to death



Randerath (amended)

The relevant follow-up information must subsequently be communicated within an additional 8 days.

Diagram 8: The Sponsor's Reporting Obligations for relevant follow-up information for cases that are life threatening or have lead to death

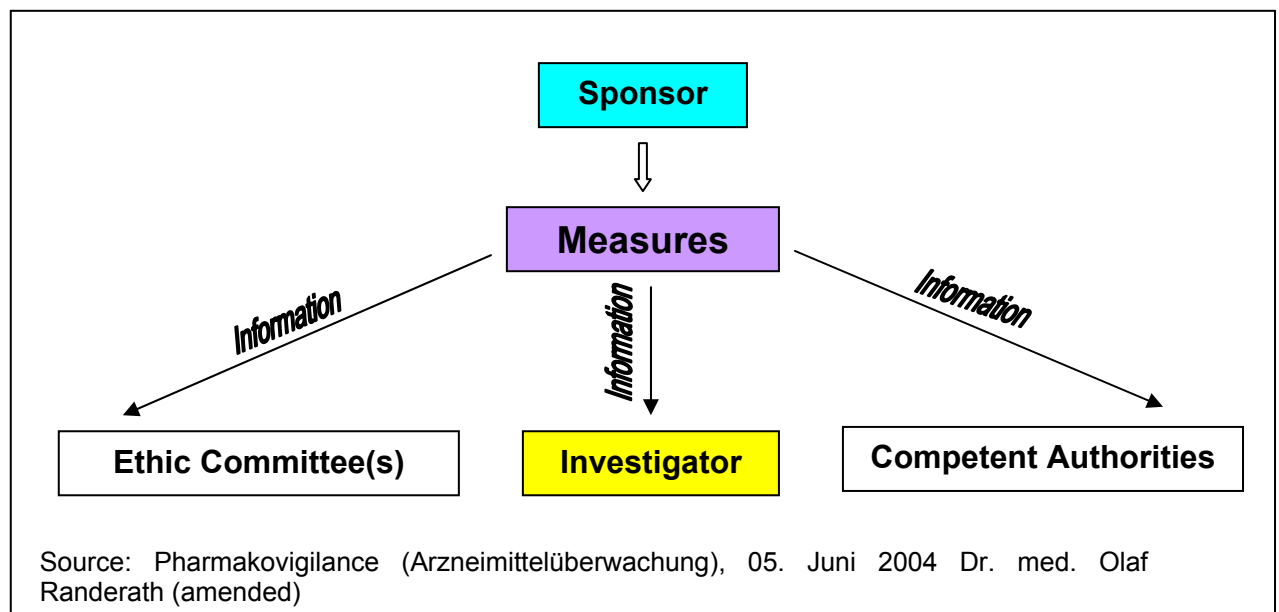


The new reporting obligations of SUSARs for the sponsor are therefore²⁶:

- **SUSAR:** Immediately, or at the latest within 15 days
- **SUSAR, fatal or life threatening:** Immediately but no later than 7 days. Relevant follow-up information within an additional 8 days
- **SUSAR, scientific assessment:** May be submitted after the deadline of 15 days

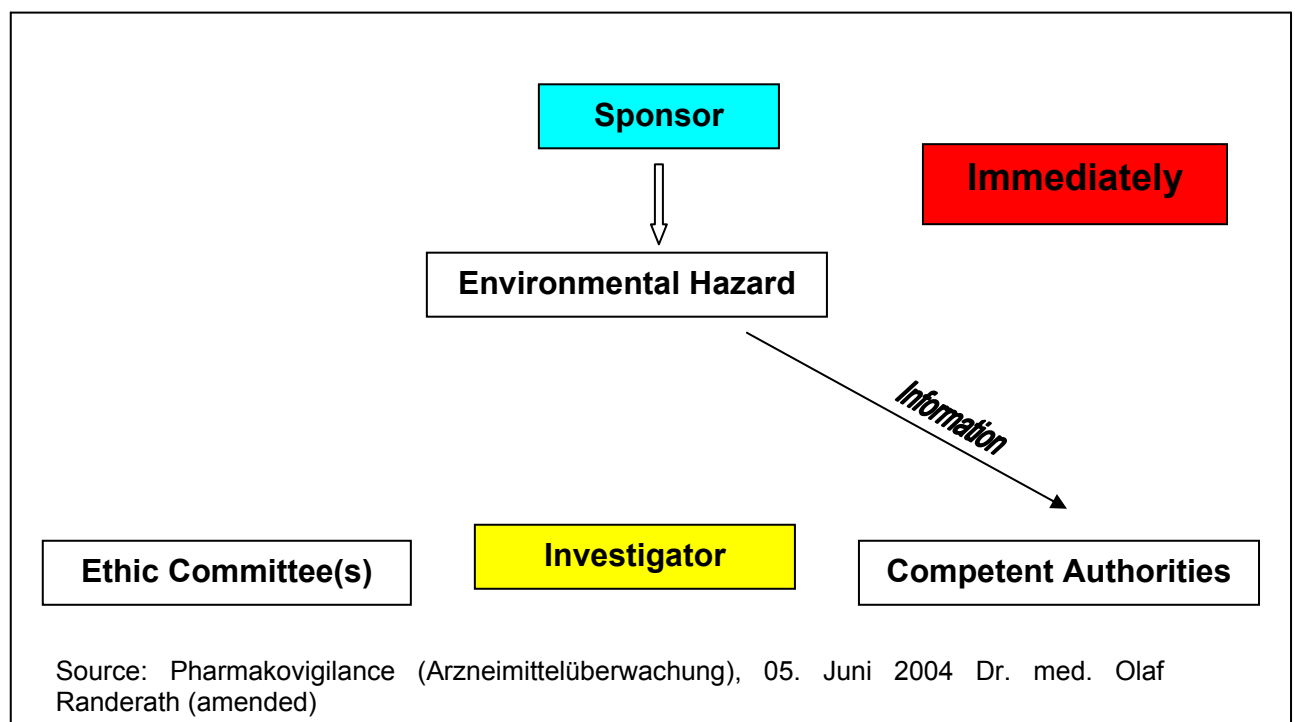
Measures taken for the protection of the remaining clinical trial subjects including reasons for these measures must be notified to the competent higher federal authority, to the ethic committee(s), to the investigator and to the competent authorities in the Member States in which the trial is being conducted by the sponsor.

Diagram 9: The Sponsor's Reporting Obligations for measures taken for the protection of subjects



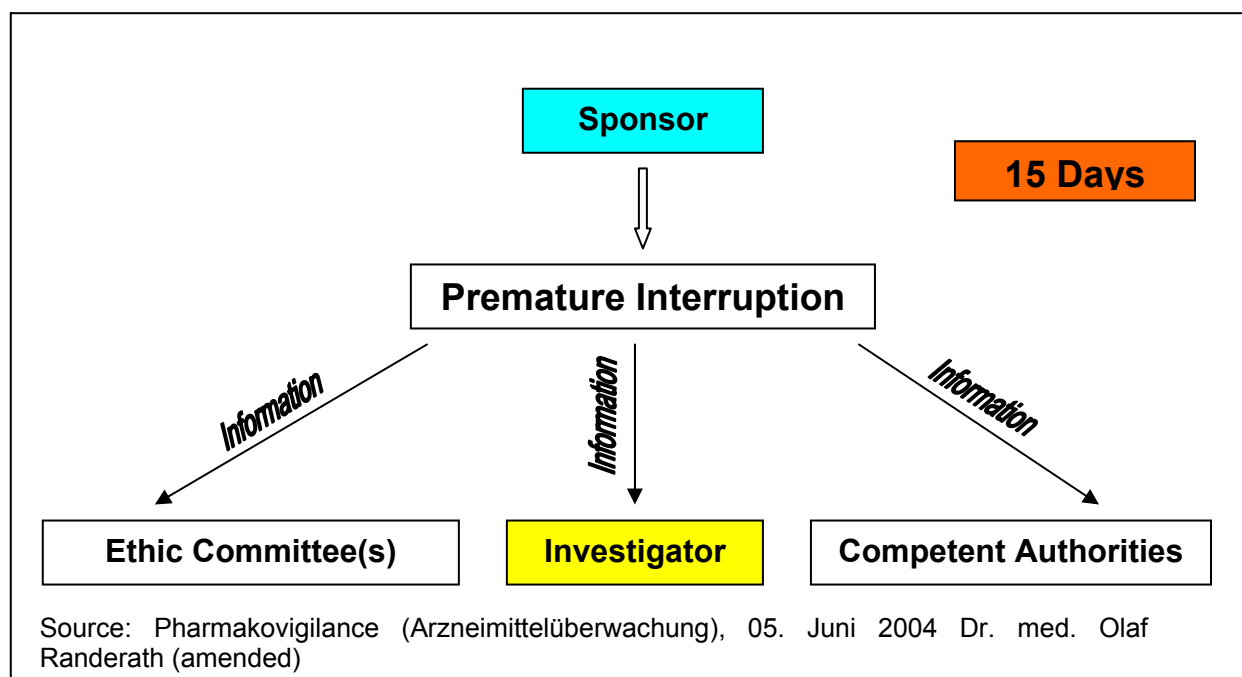
The sponsor must report environmental risks associated to medicinal products containing genetically manipulated organisms immediately to the competent higher federal authority.

Diagram 10: The Sponsor's Reporting Obligations for environmental risks



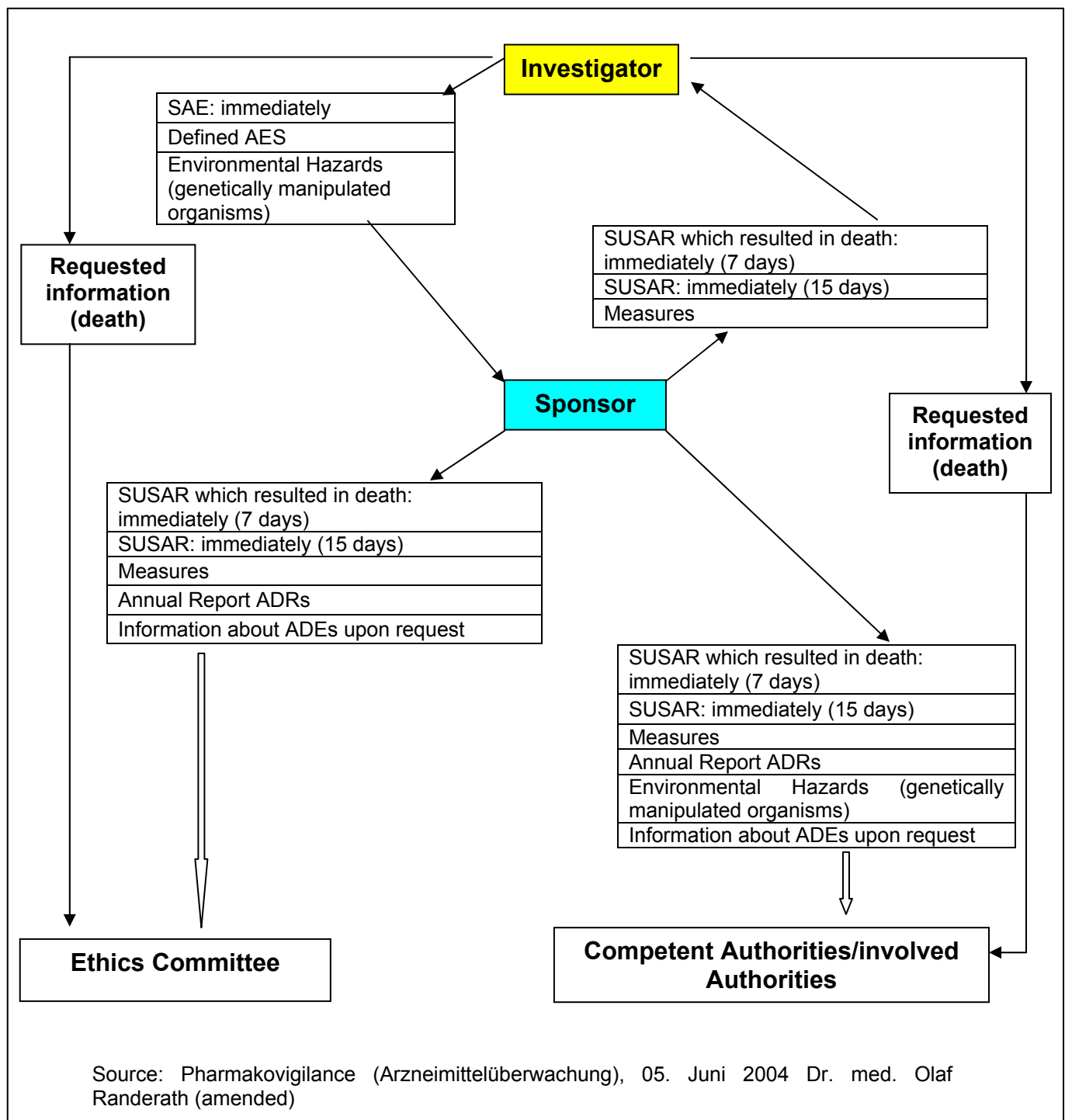
In addition, the sponsor must provide the competent higher federal authority, the Member States of the EU and EEA in whose territory the clinical trial is being conducted and the competent ethics committee, once a year throughout the clinical trial or upon request, with a listing of all suspected serious adverse drug reactions which have occurred during the trial and a report of the subjects' safety. The end or suspension of a clinical trial must be notified to the various competent authorities, the competent ethic committee, the investigator and the competent authorities of the Member States, in which the trial was conducted, within 90 days and within 15 days, with reasons, if the trial was interrupted prematurely.

Diagram 11: The Sponsor's Notification Obligations for premature interruptions of clinical trials



A summary of the report for the clinical trial, which contains its major results, must be submitted to the competent higher federal authority and the competent ethic committee within one year after the end of the trial. The sponsor must ensure that all fundamental documents for the clinical are kept for at least 10 years. These obligations ensure that important information concerning the safety of an investigational medicinal product is not lost but is available to the competent authorities and the ethic committee during the study and also for a long period after the end of study.

Diagram 12: Summary of the Investigator's and Sponsor's Notification Obligations



Competent higher federal authority:

The competent higher federal authority must notify the competent surveillance authorities, the competent ethics committee as well as the European Commission about measures taken to counteract risks, stating reasons and must supply all relevant documents to the competent surveillance authorities if required.

Advancement in pharmacovigilance during clinical trials is the obligation of the

competent higher federal authority to enter immediately, all suspected unexpected serious adverse drug reactions of an investigational medicinal product in a European database called EudraVigilance database. The EudraVigilance database is set up at the EMEA and was launched in December 2001. It contains two reporting modules to support the Pharmacovigilance activities in the pre- and post- authorisation phase:

- The EudraVigilance Post-Authorisation module (EVPM) designed for post-authorisation ICSRs as required by Council Regulation No. 2309/93/EEC, as amended (to be replaced by Regulation (EC) No 726/2004 in November 2005), Directive 2001/83/EC, as amended, and Volume 9 of the "Rules Governing Medicinal Products in the European Union".
- The EudraVigilance Clinical Trial (EVCTM) Module designed for pre-authorisation SUSARs as required by Directive 2001/20/EC²⁷.

For all clinical trials that commenced in the community from 1 May 2004 onwards, sponsors need to obtain a EUDRACT number from the EUDRACT database²⁷. In accordance with Article 24 of Regulation (EC) No 726/2004, adverse drug reactions have to be transmitted electronically as from 20th November 2005²⁸. The EudraVigilance Clinical Trial Module is only relevant for clinical trials taking place in the EU (i.e. which have been allocated an EUDRACT number). ADEs from other clinical trials will also be reported into the Eudravigilance database but not into the clinical trials module⁶⁴.

The central collection of data in the Eudravigilance database will, in addition to the other new regulations, allow a better flow of information about adverse drug reactions throughout Europe between the involved parties and therefore enhance the safety of both investigator medicinal products and approved medicinal products.

4.3.4 Organisation (Section 62 AMG)

Minor amendments have been made to section 62 of the German Drug Law. Section 62 deals with the responsibilities of the higher federal authority *to record centrally and evaluate those risks occurring during the administration of drugs, in particular adverse drug reaction, interactions with other products, contraindications and adulterations and to co-ordinate the measures to be adopted in accordance with the present law*¹¹. In the 12th amendment of the German Drug Law, contraindications have been deleted from the lists of risks, which the higher federal authority is to record and evaluate because contraindications in themselves are not hazards caused by medicinal products, but are included in the product information in order to avoid them. This amendment also takes into account the regulation found in article 73 of Directive 2001/82/EC²⁹.

Pursuant to section 62 AMG, the higher federal authority *shall act in co-operation with the agencies of the WHO, the drug authorities of other countries, the health and veterinary authorities of the federal states (Laender), the drug commissions, the chambers of the health professions and others who, in the execution of their work, keep records on drug risks in the interest of preventing direct or indirect hazards to human or animal health*. In the 12th amendment of the AMG, the EMEA and national pharmacovigilance centres have been added to list of institutions for co-operation and the purpose for the co-operation has been extended to include prevention of potential risks to the environment due to the use of a veterinary product.

The addition of the EMEA takes into account the development in practice²⁹. It is important because of its central function in collecting reports of suspected

* 11th German Drug Law

unexpected serious adverse drug reactions in the EudraVigilance database.

A net of national pharmacovigilance centres is to be established until 2010 with the aim of improving the identification of adverse drug reactions to medicinal products³⁰. The reason for this is that the quality of spontaneous reports about adverse drug events is often poor. This makes it difficult to determine the causality between the medicinal product and the adverse event. It also makes it impossible to determine the frequency of adverse drug reactions²⁹. Often the physicians are not willing to report an adverse reaction or to give further details, which would be necessary for the proper assessment of the reaction. One reason for this could be, for instance in the case of off-label use, the fear of legal consequences due to the off-label-use (see point 6 for further reasons).

In Germany, most of the reporting of adverse drug reactions is done by the pharmaceutical industry, probably because of the legal obligations to do this.

The disadvantages of the current reporting system could be met by sensible complements to the existing structure²⁹. This is becoming more important now than ever before because of the speedy advancement in the globalisation of the market for medicinal products as discussed under point 2.1. The scenes around Lipobay, Hormones during menopause or Coxibe show this very clearly³¹.

The target of the national pharmacovigilance centres, which are going to be established according to the French example³¹, is going to be to actively look for adverse drug reactions based on hospitalisation, serious diseases or specific patient groups. The centres are not going to be based on spontaneous reports but their data will be valuable complements to these. BfArM is currently working together with 6 pharmacovigilance centre models. In 2002, 1,500 well-documented adverse drug reactions were reported directly to BfArM by these centres, without the co-operation of the pharmaceutical industry. In addition, it was possible to estimate the frequency of adverse reactions using regional prescribing data. The centres also identified the need for training to avoid adverse drug reactions. BfArM can use these important pieces of information, gained by pharmacovigilance centres, for answering questions concerning pharmacovigilance²⁹.

It is planned that the current German regulatory authority, BfArM, be changed into a medicines agency called Deutsches Institut für Arzneimittel und Medizinprodukte (DAMA). The plan is for DAMA to have a federal agency for Pharmacovigilance which in turn would form a pharmacovigilance commission. The role of the pharmacovigilance commission would be to advise the federal agency for Pharmacovigilance on the assessment of drug hazards when this would be required by the agency. The members of the pharmacovigilance commission are to consist of representatives from the national pharmacovigilance centres, among others³². By working closely together with the national pharmacovigilance centres in this way, the new agency could make very good use of the knowledge gained by the pharmacovigilance centres and this would lead to an improvement in pharmacovigilance. The draft of the law for the conversion was adopted by the federal cabinet (Bundeskabinett) on 13. April 2005. However, because of possible early elections in September 2005, it will no longer be taken to the German parliament (Bundestag) before the possible elections have taken place.

4.3.5 Graduated plan (Section 63 AMG)

Section 63 AMG states that *the federal Ministry shall, by means of general administrative regulations subject to the approval of the German parliament*

(*Bundesrat*), draw up a graduated plan detailing the execution of tasks in relation to preventing direct or indirect hazards to human or animal health, as indicated in section 62 AMG (see also point 2.3).

No change has been made to section 63 of the 12th amendment of the German Drug Law. However, the almost 14 years old graduated plan, which came into force on 4 March 1990, has been amended to accommodate the changes which have been made to EU and national legislation. It came into force on 10 February 2005, one day after the promulgation in the *Bundesanzeiger* and is the third version of the graduated plan.

The new graduated plan takes into account the new marketing authorisation procedures (the mutual recognition and the centralised procedures) in the EU and amendments of the German Drug Law such as the introduction of the option for the competent higher federal authority to inform the public about drug hazards and the planned measures to reduce these risks (section 62, subsection 3 AMG)⁵⁶. It also takes into account the inclusion of the pharmacovigilance centres in section 62 of the 12th amendment of the AMG (see also point 4.3.4) and also includes the patient agent in the list of authorities and organisations with which the competent higher federal authorities works to prevent drug hazards. Furthermore, the new definition for drug interactions and the cancelling of contraindications as a type of drug hazard has also been incorporated into the new graduated plan, among others.

The criterion for initiating the two steps of the graduated plan is the degree of the possibility for a health hazard. One major change in the new graduated plan is the threshold for initiating the second step of the graduated plan, which involves the hearing of the pharmaceutical company on intended measures to reduce a drug hazard. Formerly the threshold was the founded suspicion of danger to health. Now the threshold is an ample suspicion of danger to health. According to the explanatory text, the benefit-risk balance of the medicinal product must be affected negatively as well for an ample suspicion of a danger to health since a medicinal products always bears risks⁵⁷. The regulation now also mentions an additional reason for initiating step II of the graduated plan, which is when the pharmaceutical company has not initiated the necessary measures himself to reduce a drug hazard⁵⁷. This adds more pressure on pharmaceutical companies to initiate appropriate measures on time before the authorities do this.

The drafted explanatory text for the new graduated plan mentions that the new plan also takes into account the practical experience of the authorities in the surveillance of the safety of medicinal products and that the goal for the new administrative regulation is to improve practicability through a reduction in bureaucracy⁵⁷. Further details of the amendments to the graduated plan will not be described in this thesis, as this would go beyond its scope.

4.3.6 Rearrangement of the reporting responsibilities (Section 63b AMG)

An important change which has taken place in the 12th amendment of the German Drug Law is that the reporting responsibilities of drug hazards have been deleted from section 29 of the old AMG and have been added to the 10th chapter of the Drug Law *Observation, Collection and Assessment of Drug Hazards*. A new section has now been added to chapter 10 of the Drug Law being *section 63b, Documentation and Reporting Responsibilities*. This section is divided into 8 subsections, which shall be discussed below. This change has also led to the issue of the drafted 4th Promulgation Concerning Reporting Obligations pursuant to section 63b subsection 1 to 8 AMG of 15th June 2004 by BfArM and PEI (4. Bekanntmachung zur Anzeige von

Nebenwirkungen, Wechselwirkungen mit anderen Mitteln und Arzneimittelmisbrauch nach §63 Abs. 1 bis 8 des Arzneimittelgesetzes (AMG) vom 29. April 2005). The Promulgation Concerning Reporting Obligations has always been issued by the federal ministry of health (BfArM) and later, after its division, by BfArM and PEI and serves as a concretisation and interpretation of the laws governing reporting responsibilities. The 4th Promulgation Concerning Reporting Obligations replaces the 3rd Promulgation Concerning Reporting obligations pursuant to section 29 AMG, which was actually an interpretation of the 5th AMG. The interpretations in the new Promulgation are based on the modernised regulations in the AMG, on Directive 2001/83/EC and international recommendations such as Volume 9 - Pharmacovigilance and the guideline "Post-Approval Safety Data Management - Definitions and Standards for Expedited Reporting (CPMP/ICH/3945/03)"³⁴. The details of this new notice are not going to be dealt with in this thesis as this would go beyond its scope. However, a few details will be mentioned to complement the described changes in the AMG.

4.3.6.1 Recording of adverse drug effects, volumes of sales or prescriptions and withdrawals from the market (*sub-section 1*)

According to the new section 63b, subsection 1 of the amended German Drug Law, it is the responsibility of the marketing authorisation holder to *"keep detailed records of all suspected cases of adverse drug reactions that have occurred in the Community or in a third country including information about the delivered quantities, for blood products also about the number of recalls."*

The responsibilities of the MAH have been taken over from the old section 29 of the AMG. However, while the old law contained only the general statement: *he shall keep a record of all suspicious cases other than serious side effects or interactions with other substances of which he is informed by a member of a health profession*, the new section 63b, subsection 1 clearly states that the MAH is responsible not only for keeping records concerning adverse drug reactions that have occurred in Germany but also concerning those that have occurred within the Community and third countries. Under the old law, the responsibilities concerning ADRs that occurred outside Germany could be deduced from the 3rd Promulgation Concerning Reporting Obligations according to section 29 AMG³³ but now these have been added to the binding law in a clear statement. It also takes into account the efforts being taken in respect of having one market in the EU.

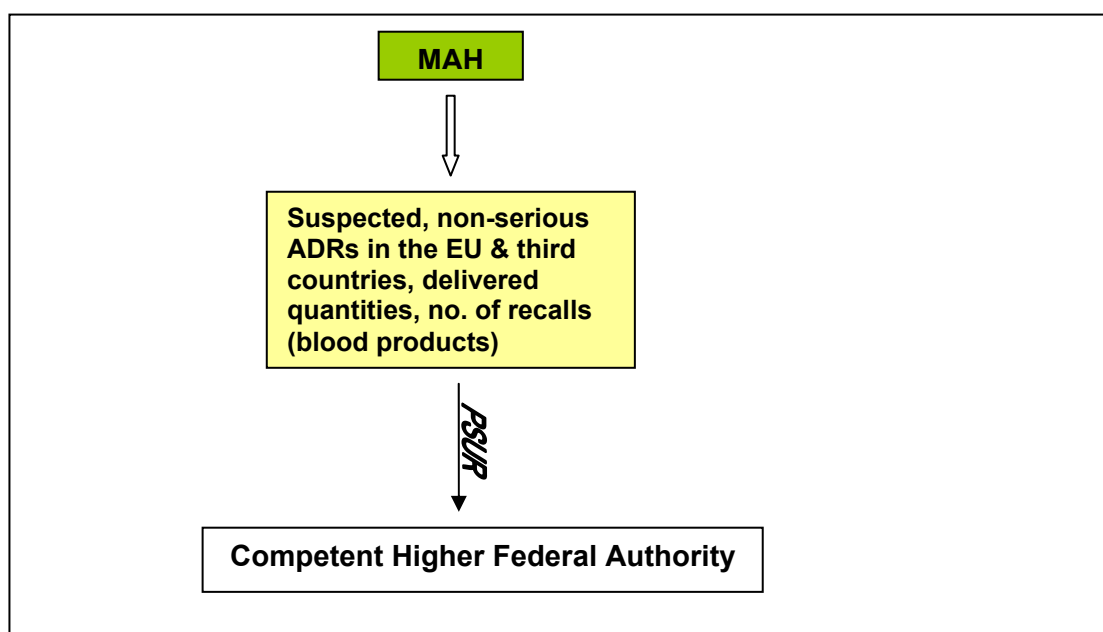
The source of information for ADRs, for which records should be kept (a member of a health-care profession), has been omitted in the amended law. The 4th Promulgation Concerning Reporting Obligations pursuant to section 63b AMG explains which actions should be taken if the information was not obtained from a health professional. As a result, disclosure requirements may arise for ADRs which were not reported by a health professional but which have either later been confirmed by a health professional or for which there are enough meaningful details or which has been judged as being an ADR by the commissioner for the graduated plan or by the qualified person. This is in accordance with EU regulations (Directive 2001/83/EC, Article 104 no. 1), which states that *"the marketing authorisation holder shall be required to maintain detailed records of all suspected adverse reactions occurring in the community or in a third country"*. The ICH guideline "Post-Approval Safety Data Management" states that *"Emphasis should be placed on the quality of the report and not on its source. Even if the reports received from consumers do not qualify for regulatory reporting, the cases should be retained."*³⁶ Even though the 3rd Promulgation Concerning Reporting Obligations according to section 29 AMG³³, under 2.12 also stated that disclosure requirements may arise for ADRs which were

not reported by a health professional, the deletion of the phrase “*of which he is informed by a member of a health profession*” in the law helps to clarify the course of action for such cases. The proper dealing with information which may have been received for instance from a patient, his relatives or a lawyer is very important in order to prevent the loss of important information concerning the safety of a drug and about the frequencies of ADRs. The importance of this becomes clearer in the light of the fact that health-care professionals do not report many adverse drug reactions at all, as mentioned under points 4.3.4 and 6.

The obligation to keep details about the number of recalls in relation to blood products is new in the AMG. It is the transposition of Artikel 13, paragraph 1 and annex II of Directive 2002/98/EC³⁵ into national law.

Reports of non-serious adverse reactions are normally submitted to the authorities in tabular form (line-listings) with the Periodic Safety Update Report (PSUR) and not as individual case reports. The PSUR will be discussed under point 4.3.6.5. It is important to note that according to the 4th Promulgation Concerning Reporting Obligations, cases where only the active substance is known, i.e. the MAH is not sure if the medicinal product under which the ADR occurred is actually his, must also be submitted within the PSUR and data must therefore be collected. This regulation should probably help to prevent the loss of information.

Diagram 13: Reporting Obligations for suspected non-serious ADRs



4.3.6.2 Reporting responsibilities (*sub-section 2*)

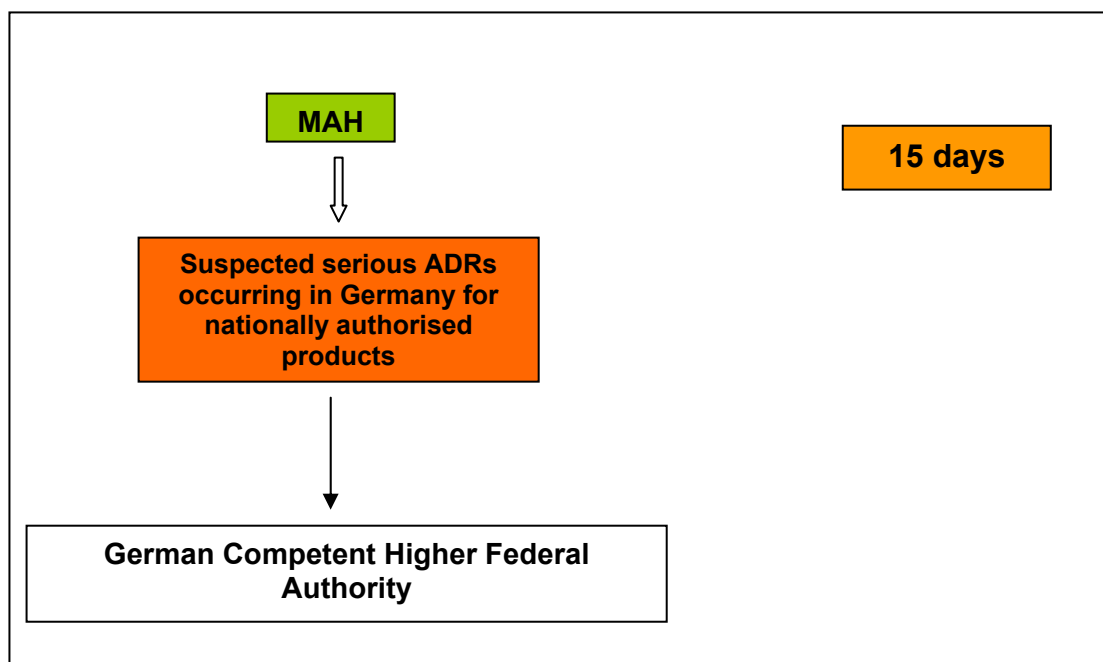
Sub-section 2 deals with reporting obligations for serious adverse drug reactions to national and international authorities.

According to sub-section 2 sentence 1, the MAH must “*inform the competent higher federal authority immediately, or at the latest within 15 days of its coming to his knowledge, of any case of suspected serious adverse drug reactions*” which occurred in Germany. This regulation has been taken over from the former section 29 AMG and is equivalent to the regulation found in directive 2001/83/EC, Article 104 no. 2,

except for the fact that Directive 2001/83/EC talks explicitly about suspected serious adverse drug reactions “*which are brought to his attention by a health care professional*” and the Rules Governing Medicinal Products in the EU, Volume 9 – Pharmacovigilance, point 1.2.2.1 (i) “*Serious Adverse Reactions occurring within the European Community*” talks about the MAH reporting, on an expedited basis, “*all serious adverse reactions occurring within the Community and brought to its attention by a health-care professional*” to the competent authority in the Member State in whose territory the incident occurred. It goes on to say, under point 1.2.2.1(iii), that all other reports do not need to be reported on an expedited basis, but should be reported on request or as line listings according to the section on periodic safety update reports, section 1.4”.

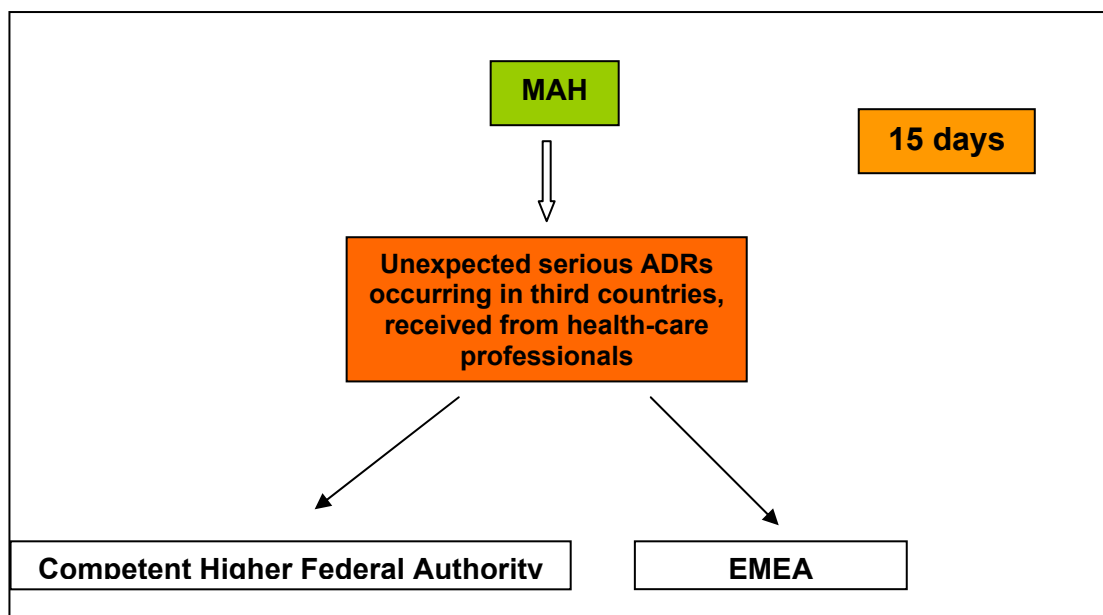
The German law therefore goes beyond the EU regulation in this particular case. It is not compliant with the harmonisation of regulations governing medicinal products in the EU and adds to the workload of pharmaceutical companies. On the other hand, this regulation may prevent important information from getting lost for the reasons already stated above.

Diagram 14: Notification obligations for suspected serious ADRs occurring in Germany



Sentence 2 a and b refer to cases which have been received from third countries. Sentence 2 a refers to suspected unexpected serious adverse reactions: the MAH “*shall report immediately, but no later than 15 days, all suspected unexpected serious adverse reactions, which did not occur in a Member State of the EU, and which were brought to his attention by a health care professional, to the competent higher federal authority and the European Agency for the Evaluation of Medicines*”. This has been taken over from Directive 2002/83/EC and only refers to cases received from a health care professional as intended by the European law.

Diagram 15: Notification Obligations for unexpected serious ADRs occurring in third countries



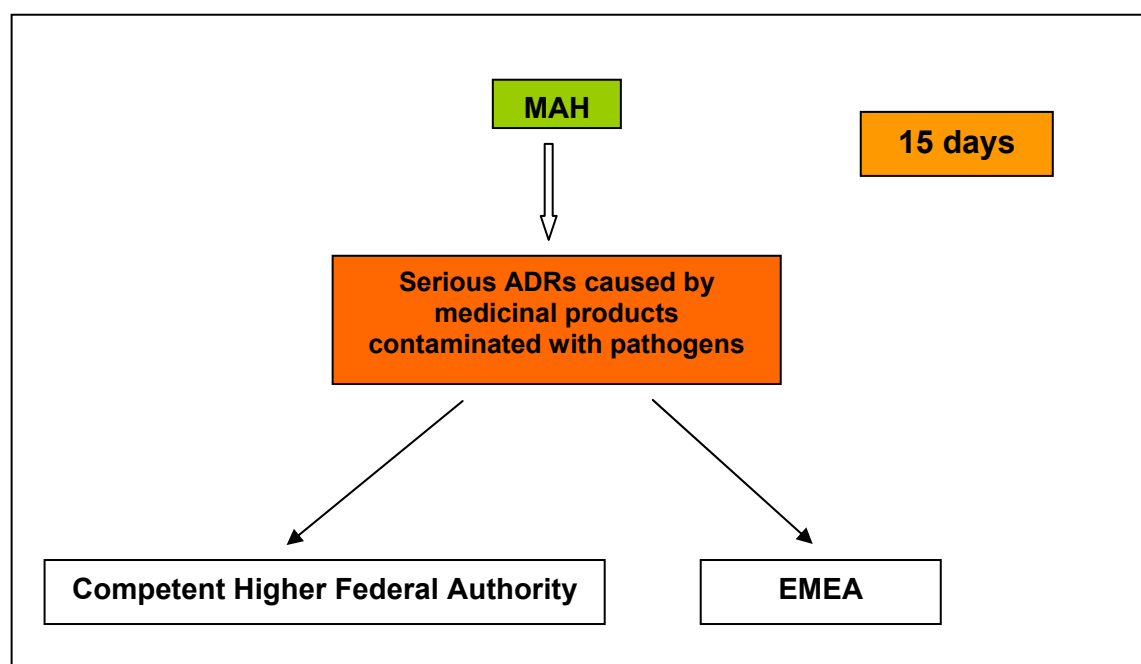
The fact that only those adverse reactions that are unexpected and serious at the same time must be reported is of importance for improving the assessment of the benefit risk ratio of medicinal products. In 2002, about 211 000 reports on adverse drug reactions were submitted to BfArM. Of these, 204 000 reports were submitted by pharmaceutical companies, about 3 000 were submitted by the drug commissions of German medical doctors, pharmacists as well as dentists and about 1 700 reports were submitted directly by medical doctors. Of the 204 000 cases which were reported by pharmaceutical companies, 164 000 reports originated abroad and only 31 000 reports originated in Germany, while 9 000 cases were literature reports. These figures show that about half of the reports that are submitted to BfArM originate in third countries. Because of this large (and probably unmanageable) number of cases, a restriction to report only unexpected serious adverse reactions will help the competent authorities to focus and concentrate on those cases which are really critical³⁹.

Sentence 2 b says that for medicinal products which contain constituents from raw material derived from human beings or animals, every suspected infection which has come to the knowledge of the MAH and *“which is a serious adverse reaction and was caused by the contamination of these medicinal products with pathogens and did not occur in a Member State of the EU”* must be reported to the competent higher federal authority and the European Agency for the Evaluation of Medicines immediately, but no later than 15 days. This addition to the law is not found in Directive 2001/83/EC. Article 104(4) of the amended directive (2004/27/EC) contains the requirement that *“the MAH shall ensure that all suspected serious unexpected transmissions via a medicinal product of any infectious agent occurring in the territory of a third country are reported promptly in accordance with the guideline referred to in Article 106(1)...”*. However, this regulation only refers to unexpected transmissions of infectious agents, while the 12th amendment requires every case to be reported. This regulation was added because of interventions from the Paul-Ehrlich Institute, even though it is not in line with the harmonisation efforts of pharmacovigilance in the EU, and should ensure that the competent higher federal authorities continue to be informed about blood products from third countries, which are contaminated with

HIV²⁰. The importance of this becomes evident in the light of the catastrophe in the 1980ies, when HIV contaminated blood products lead to the infection of mostly haemophilia patients with the virus. According to the data published by the 3rd enquiry board of the lower house of German parliament, during the early 80ies till 1993, the HI virus infected 43.3% of treated haemophilia patients. In figures, this means of the 3 135 patients treated, 1 358 were infected with the virus^{37*}. The reporting obligations of serious adverse reactions with blood products, occurring in Germany, are covered by the Law on Transfusion (Gesetz zur Regelung des Transfusionswesens).

The inclusion of raw material derived from animals could be linked to contamination caused by BSE agents²⁰.

Diagram 16: Notification Obligations for serious ADRs caused by medicinal products contaminated with pathogens



The new laws do not mention adverse drug reactions that have occurred in other Member States of the community. The reason for this is the European concept of a central database for adverse drug reactions to which all competent authorities of the Member States have access. Every Member State must ensure that all suspected cases of adverse drug reactions, which occurred in his territory, are fed into this central database. The reporting of ADRs to each Member State therefore becomes unnecessary.

Sentence 3 contains a further national addition, which does not have any corresponding law in the European legislation. According to sentence 3, the MAH must report to the competent higher federal authority *“frequent abuse or individual cases of substantial abuse, if this can directly jeopardise human or animal health”*. This law was taken over from the former section 29 AMG. The 4th Promulgation

* Bericht des 3. Untersuchungsausschusses, Drucksache 12/8591, HIV-Infektionen durch Blut und Blutprodukte, S. 198ff is mentioned by the authors of Hintergrundpapier des Verbraucherzentrale Bundesverbands e.V. zur Änderung des Arzneimittelhaftungsrechts.

Concerning Reporting Obligations defines drug abuse to mean *the persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful or psychological effects*. This definition has been taken over from Directive 2001/83/EC, Article 1(16). However, since there is no differentiation according to the severity of the abuse nor according to where the abuse occurred nor the source of information, this is the most extensive regulation under section 63b AMG²⁰ and goes beyond the EU regulations. The Rules for Governing Medicinal Products in the EU, Volume 9 – Pharmacovigilance, states: *“The MAH should report cases of overdose and abuse that lead to suspected serious (EU) or serious unexpected (outside EU) ADRs on an expedited basis to the appropriate competent authority...Reports of overdose and abuse with no associated adverse drug reactions should not be reported as adverse reactions”* (point 1.3.6 “Reporting of overdose and abuse”). This corresponds to the way ADRs should be reported under section 63, sub-section 2, sentence 1 and 2 AMG (i.e. suspected serious cases occurring in Germany and all serious unexpected cases of ADRs from third countries. Those cases occurring in the Member States should be taken from the EU database³⁹. The discrepancy here is again not in line with the harmonisation efforts of the rules governing pharmacovigilance in the EU. Furthermore, the EU regulation states that ADRs resulting from abuse should be reported, not just the abuse as stated in the AMG³⁹.

The reporting of serious adverse reactions is done in the form of an individual case report. The minimum criteria for reporting are:

- An identifiable patient
- An identifiable reporter
- A suspect product and
- An adverse reaction

A change in the definition of the minimum criteria for qualifying a patient as identifiable has been made in the 4th Promulgation Concerning Reporting Obligations. Instead of the former two, now only one of the following qualify a patient as identifiable: Initials, date of birth, age, gender, patient identification number. This is in line with the Note for Guidance on Definitions and Standards for Expedited Reporting and is an improvement because it prevents loss of important information due to cases that do not qualify as an individual case report because of lack of data. The availability of data is often restricted, not only when the case is reported initially but also later, because of a lack of cooperation and willingness to report by health professionals.

Criteria for qualifying a reporter as an identifiable one have also been introduced in the 4th Promulgation Concerning Reporting Obligations. Here too, only one of the following data is necessary: Name or initials, address, qualification.

The obligations according to sub-section 2, sentence 1 and 2b are also valid for adverse reactions in humans caused by the application of a medicinal product for animals.

It is also important to note that the 4th Promulgation Concerning Reporting Obligations sets out reporting obligations for special cases:

1. It states that the competent higher federal authority expects the MAH to follow up on cases of pregnancy reported by medical professional, during which one of its medicinal products is used. If such a report originates from a patient, the MAH should try to obtain details from the physician. If there is a suspicion that the mother experienced any adverse drug reactions or that the use of the medicinal product caused a congenital anomaly/birth defect, this must be reported to the competent higher federal authority.
2. It describes which cases of loss of efficacy must be submitted with the PSUR,

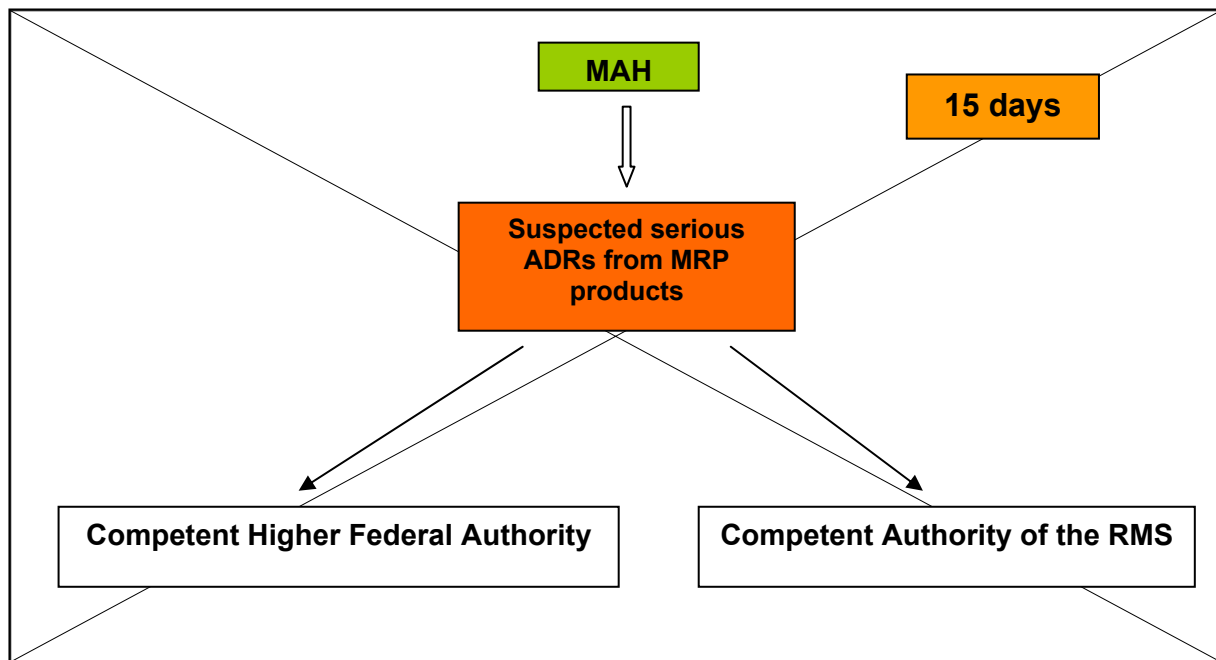
which ones must be reported within 15 days (expedited reporting) and in which cases the competent higher federal authority should be notified independent of the reporting of individual cases

3. It goes on to say that reports about adverse and unintended reactions following over dosage of a medicinal product should also be reported on an expedited basis (within 15 days). This also applies to cases where the medicinal product was used to commit suicide or the attempt was made to commit suicide or where there is a suspicion that the medicinal product led to the development of a suicidal emotional state.

4.3.6.3 Additional reporting responsibilities for products involved in a mutual recognition procedure (*sub-section 3*)

According to the regulation under sub-section 3, the MAH, who obtained the marketing approval through the Mutual Recognition Procedure (MRP), *“must also report immediately all suspected serious adverse reactions or adverse reactions in humans due to the application of a medicinal product for animals”* which occurred in Germany to the competent authority of the Reference Member State (RMS). According to the 4th Promulgation Concerning Reporting Obligations, this means within 15 days. Due to the process of harmonisation of legislation in Europe, there should be similar legislation in place in the other Member States for the reporting of such reactions, which have occurred in these other States to the competent higher federal authority in Germany, if Germany is the RMS¹⁶.

Diagram 17: Notification Obligations for medicinal products involved in a mutual recognition procedure



4.3.6.4 Submission of further documents, scientific evaluation (*sub-section 4*)

According to the 4th Promulgation Concerning Reporting Obligations, individual case reports should be reported to the competent higher federal authority using the forms

from BfArM or PEI or the CIOMS form (see annex). In addition to this, according to sub-section 4, *all existing documents which are necessary to be able to assess suspected cases or cases of observed abuse as well as a scientific evaluation thereof shall be submitted to the competent higher federal authority*. This means that the reporting obligations have not been fulfilled completely until a scientific evaluation has been submitted¹⁶.

This regulation has also been taken over from the former section 29 AMG. However, the obligation of submitting a scientific evaluation is found only in a few Member States of the EU²⁰. The additional documents, which should be submitted, are now further specified in more detail than before in the 4th Promulgation on Reporting Obligations. It also recommends the use of the Criteria of the WHO Collaborating Centre for International Drug Monitoring only for causality assessment and no more the criteria “A”, “B”, “O” of the EU as well. This should result in some more clarity and uniformity concerning the documents that are to be submitted. The explanations to this in the 4th Promulgation Concerning Reporting Obligations will not be discussed in this as this would go beyond its scope.

4.3.6.5 Introduction of Periodic Safety Update Reports (PSURs) (sub-section 5)

The introduction of Periodic Safety Update Reports (PSURs) into the German national law is one of the major changes in the field of pharmacovigilance that has been introduced with the 12th amendment of the law. The submission of PSURs was already recommended in the 3rd Notice on Reporting Obligations but has now become binding law through the transposition of the regulations found in Directives 2001/83/EC and 2001/82/EC into national legislation. Detailed guidance on the compilation of PSURs is found in the Rules Governing Medicinal Products in the European Union, Volume 9 - Pharmacovigilance.

Pursuant to the former section 29 AMG, the MAH had to keep a record of all suspicious cases other than serious adverse reactions or interactions with other substances of which a member of a health profession informed him. In so far as no condition was imposed on the contrary, he was to *“transmit these records to the competent higher federal authority forthwith upon request or at least every six months during the first two years following the granting of the marketing authorisation or immediately upon request by the competent higher federal authority”* and *“all existing documents which are necessary to be able to assess suspect cases or cases of observed abuse as well as a scientific evaluation thereof”* were to be submitted as well. This has been replaced by the obligation to submit Periodic Safety Update reports. The so-called zero reports (Null-Meldungen) by which the MAH could notify the competent higher federal authorities that no cases of adverse drug reactions came to his knowledge during a certain period of time are now also no longer sufficient for fulfilling the law⁷².

In addition, pursuant to section 49 *“Automatic Prescription Requirement”*, sub-section 6 of the old AMG, the MAH had to submit an experience report *“Erfahrungsbericht”* for medicinal products which contain substances or preparations of substances, of which the effect is not generally known in the medical sciences. This was also the case for medicinal products that contain substances of known effect but for which the effect of the formulation in the medicinal product is not generally known in the medical sciences. This report had to give details of the quantities distributed during the period under review; furthermore, new findings on effects, type and frequency of side effects, contraindications, interaction with other products, habituation, dependence or a use of the drug not complying with the intended purpose had to be included. This report had to be submitted 2 years after approval of the medicinal

product or 2 years after the renewed assignation of the substance to fall under this law.

The obligation to submit this experience report has also been deleted with the 12th amendment of the German Drug Law because it falls together with the time of submission of the 4th half-year PSUR, the PSUR being more elaborate than the experience report.

The main focus of PSURs is also adverse drug reactions. One objective of the PSUR is to establish whether the information recorded during the reporting period is in accordance with previous knowledge on the product's safety and whether changes need to be made to the product information. A PSUR normally contains information about the world-wide marketing status, update of regulatory or marketing authorisation holder actions taken for safety reasons, changes to reference safety information, patient exposure, individual case histories including the marketing authorisation holder's analysis of these individual case histories, studies, efficacy-related information and an overall safety evaluation including a conclusion. The conclusion should indicate which safety data do not remain in accord with the previous cumulative experience and with the reference safety information and specify and justify any action recommended or initiated¹⁵. Individual case histories are presented in the form of line-listings and include:

- All serious reactions, and non-serious unlisted reactions, from spontaneous notifications;
- All serious reactions (attributable to the medicinal product by either investigator or sponsor), available from studies or named-patient (compassionate) use;
- All serious reactions, and non-serious unlisted reactions, from the literature;
- All serious reactions from regulatory authorities.¹⁵

It can be seen from the description above, that the PSUR goes beyond the scope of the reports described above because its purpose is a worldwide evaluation of the benefit/risk ratio of the active substance.

Normally, all dosage forms and formulations as well as indications for a given active substance of medicinal products authorised to one MAH may be covered by one PSUR. The PSUR is therefore an instrument used for evaluating the safety of approved medicinal products containing the same active substance and are a valuable source of pharmacovigilance data for the competent authorities. This is seldom possible using just individual case reports^{15,38,54}

According to the 4th Promulgation on Reporting Obligations, suspected adverse reactions, which do not qualify as 15-day-reports, can also be submitted in the form of line-listings. However, the Rules Governing Medicinal Products in the European Union, Volume 9 – Pharmacovigilance, states that, as the collection and reporting of non-serious, listed ADRs may not be required in all EU countries, such line-listings should only be submitted as an addendum to the PSUR when requested by a regulatory authority¹⁵. This again shows that the regulations governing pharmacovigilance have unfortunately not yet been fully harmonised and this may lead to a gap in the collection of information which may in turn influence the safety evaluation of a medicinal product.

The new law for the submission of PSURs states that the PSUR must be submitted either immediately upon request or at least every 6 months for the first two years after authorisation, after that annually for the subsequent two years and at the time of renewal. Thereafter, the PSURs must be submitted at five-yearly intervals together with the application for renewal of the authorisation. However, the frequency of submission can be amended to up to five-yearly intervals when this is applied for by the MAH. This is of interest especially to marketing authorisation holders of generic

products that are normally approved on the basis of Directive 2001/83/EC, Article 10 (iii). As the active substances of these products have already been approved for at least ten years in Germany according to this legislation, it does not appear to make much sense under normal circumstances, that PSURs must be submitted for these substances at a higher frequency than every five years at the time of renewal. As the law has made provision for an adjustment of the frequency to every 5 years, it is hoped that the competent higher federal authority will be willing to grant this adjustment wherever possible. This would help pharmaceutical companies to save time and cut down on expenses, especially because generic companies usually have a very wide range of products in their portfolio. According to section 63b, subsection 5 and the 4th Promulgation Concerning Reporting Obligations, the applicant for a marketing authorisation can apply for an amended frequency for the submission of PSURs, which, when granted, would become part of the licence document. This can also be applied for after approval of the product. However, according to the Rules Governing Medicinal Products in the European Union, Volume 9 – Pharmacovigilance, point 1.4.2.5.2 (Circumstances where the PSUR submission cycle may be amended), “if an amendment is applied for after authorisation, such an application should follow the procedures for a type II variation”¹⁵. This means that the MAH has to spend time and money on a variation to amend the submission frequency. An adjustment of the law in favour of the pharmaceutical industry, for instance, that PSURs for generic medicinal products generally need to be submitted upon request or on a five-yearly basis (or on a three-yearly basis, according to the amendment of the submission intervals proposed in the drafted 14th amendment of the Drug Law, see point 5.2.5.1), should be considered.

According to the new legislation, PSURs must also be submitted for standard approvals. The question, whether users of standard approvals should also submit PSURs was cleared during the consultations of the parliament²⁰. According to the 4th Promulgation Concerning Reporting Obligations, if necessary the competent higher federal authority will request for the submission of PSURs for standard approvals pursuant to section 36 AMG separately in the *Bundesanzeiger*.

Sentence 6 of sub-section 5 is a legal obligation for the MAH of blood products to submit PSURs *“immediately upon request or, as far as recalls or cases or suspected cases of serious adverse reactions have occurred, at least once a year.”* According to the explanatory statement to this law amendment, this law takes into account the regulations in directive 2002/98/EC. The required high frequency of submission can also be seen in the light of the HIV catastrophe²⁰ in the 1980ies as discussed under point 4.3.6.2. According to the explanatory statement, this should make it possible for the competent higher federal authority to compare the information about recalls or cases or suspected cases of serious adverse reactions that were submitted throughout the year with the information submitted with the PSUR. This will probably help to ensure that there is no loss of information. In addition, it adds pressure on the MAH to be diligent in the surveillance of his blood products.

4.3.6.6 Co-operation of the higher federal authorities with the EMEA (sub-section 6)

This law is a legal obligation for the competent higher federal authorities to report every suspected serious adverse reaction which is brought to their knowledge and which occurred in Germany *“immediately but at the latest within 15 days following the of receipt of the information to the EMEA and, if necessary, to the MAH”*. As discussed earlier on, all reports on adverse reactions will be collected in a central electronic database set up at the EMEA. This law is therefore a prerequisite for the functioning of such database and must be implemented by other Member States as

well. The need for reporting adverse reactions to the competent authorities of other Member States will therefore only be obsolete when all Member States meet this requirement.

According to sub-section 6, the MAH should be informed about suspected serious ADRs “if necessary”. However, it is necessary that the MAH is always informed about such cases by the authorities³⁹. This would help the MAH in his own assessment of the risk to benefit balance of his product. It would also be of benefit to him and to the authorities if he receives a confirmation that his notification has been submitted to the EMEA as a control that no information was lost during the reporting procedure.

4.3.6.7 Reporting responsibilities for registration holders, applicants, marketing authorisation holders and for co-marketing (sub-section 7)

Sub-section 7 states clearly, that the obligations contained in sub-section 1 to 4 apply to the MAH not only when the medicinal product is on the market but also after it has been taken from the market.

The 4th Promulgation Concerning Reporting Obligations states that PSURs must also be submitted as long as a marketing authorisation exists in *German* and/or if Germany acts as the RMS for products, which were authorised through the decentralised procedure.

Sub-section 7 also states that the obligations contained in sub-section 1 to 4 also apply to the applicant of a marketing authorisation i.e., as soon as the application for marketing authorisation has been submitted to the competent federal authority. This is a special feature in the German law and has been taken over from the old section 29 AMG. According to the Rule Governing Medicinal Products in the European Union, Volume 9 – Pharmacovigilance, point 1.3.1, *“Reporting in the Period between the Submission of the Marketing Authorisation Application and the Granting of the Marketing Authorisation”*, in the period between the submission of the marketing authorisation application, but prior to authorisation, *“routine single case expedited reporting is not required except according to national law where a product is being used under clinical trial”*. This law can therefore be understood as applying to reports originating from clinical studies. However, it goes on to say that information which impacts the benefit/risk evaluation of the product *“may become available from the applicant or Member State where the drug is already in use on a compassionate basis, or from countries where the drug is marketed”*. Such information that becomes available to the applicant should be submitted immediately to the competent authorities where the application is under assessment or to the EMEA, rapporteur and co-rapporteur in the case of a centralised application. It also says that what constitutes a change to the benefit risk balance is a matter of judgement for the applicant but that the applicant may be required to justify a decision not to report. In other words, the German national law requires applicants to collect and report ADRs during the assessment period while this is only required on the EU level in certain cases. From a safety point of view, it makes sense to apply the reporting obligations to applicants as well in order to avoid the loss of important information which may have had impact on the benefit/risk evaluation of the product but which was not clear to the applicant at that point in time. Apart from this, the competent authority can make itself a picture of the safety of the product independent of the applicant, who is normally very interested at this point in time to receive the marketing approval for the product. It also gives more security to the applicant if he must not justify a decision for not reporting a case at a later point in time.

Furthermore, the new law clearly states that the obligations under sub-sections 1 to 4

also apply to registration holders but the obligation to submit PSURs does not. It also states clearly that the obligations under sub-section 1 to 5 also apply to pharmaceutical companies, which distribute a medicinal product, but are not the owners of the marketing authorisation (this applies for instance to co-marketing or distribution agreements). However, it goes on to say that it is possible for the pharmaceutical company that is not the owner of the marketing approval to transfer its obligations in part or as a whole on the MAH. To be valid, this must be done in writing. In this case the other company must report any ADRs that come to his knowledge to the MAH but the 15-day deadline begins when the MAH has received the minimal criteria for reporting ADRs. However, the 4th Promulgation Concerning Reporting Obligations states that the competent federal authorities expect that a detailed procedure is in place to ensure an immediate exchange of information between the contract partners so that the 15 day deadline can be met even if the initial report is made to the contract partner and not to the MAH. This is important in terms of pharmacovigilance and should further be enforced by law.

4.3.6.8 Reporting responsibilities for centrally approved products (sub-section 8)

This sub-section states that sub-sections 1 to 7 do not apply to medicinal products that have been approved through the centralised procedure. This is because the EU Commission regulation numbers 2309/93 and 540/95, which is the legislation for centrally authorised products, are directly binding and do not need to be transformed into national law (see annex for hierarchy of the community texts).

4.3.7 Empowerment to issue regulations for procedures (Section 80 AMG)

Section 80 of the amended AMG empowers the federal ministry to regulate “*by means of ordinance which does not need to be approved by the Bundesrat, the further details concerning the procedure for reporting of drug hazards*”. According to the explanatory statement to the drafted 12th amendment of the German Drug Law, section 80 is an aggregation of the empowerments under the former section 35, sub-section 1 and section 36, sub-section 3 into one central regulation. Especially the empowerment for procedures for reporting drug hazards is further specified²⁹. It also mentions that rules for forwarding reports, the number of copies to be submitted and the electronic submission of reports can be set out by the federal ministry. The federal ministry can transfer this empowerment to the competent higher federal authority without approval by the chamber of parliament representing the federal states (Bundesrat). The fact that the chamber of parliament representing the federal states does not need to approve these regulations may be positive on the one hand because it may facilitate a quicker issue of regulations governing the reporting of drug hazards. On the other hand it may also have a negative impact on the pharmaceutical industry because it does not leave much room for the pharmaceutical industry to influence these regulations. This may have financial consequences. For instance, an obligation to use MedDRA terminology for reports would pose a big financial problem for small and middle sized companies²⁰, although MedDRA terminology would help to harmonise the terminology used for reports of drug hazards which in turn would help in the proper assessment of risks. Special computer software could also pose financial problems and elaborate procedures may require more man power than the companies can afford. A statement that the financial interests of the pharmaceutical industry should be adequately considered, should have been added here to protect the interests of the pharmaceutical industry³⁹.

4.4 Coming into force

The 12th amendment of the German Drug Law was adopted by the German parliament (Bundestag) on 2 April 2004 and by the chamber of parliament representing the federal states (Bundesrat) on 9 July 2004. It came into force on 6 August 2004.

However, some of the regulations of section 63b were exempted from coming into force, the reason being that some of these changes were based on the establishment of a functioning electronic database (EudraVigilance). As already discussed above, every competent authority of all Member States will enter suspected cases of adverse drug reactions into the database and will be able to search the database for adverse drug reactions that have occurred in other Member States. It was not until this database was under full function that the federal government of Germany could abandon the double reporting of cases from other Member States. To this end, the government was originally planning to exempt the whole of section 63b from coming into force⁴⁰. However the deadline for transposing the regulations governing pharmacovigilance from Directive 200/38/EC into national law was 5 December 2001 as discussed under point 4.1. This and other international obligations led to the decision that parts of section 63b would come into force immediately after promulgation of the 12th amendment of the German Drug Law while the remaining parts would come into force *when the requisites for the electronic transfer of reports are in place in the Member States and it is possible for the competent authorities to conduct researches in the data network set up at the EMEA*. The federal Ministry for Health and Social Security was going to announce the day of coming into force in the *Bundesgesetzblatt*.

As a result of this arrangement, sub-section 2, sentence 2a came into force on 6 August 2004. According to this law, reports on *suspected unexpected adverse reactions, which did not occur in a Member State of the EU must be reported immediately, but no later than 15 days, to the competent higher federal authority and the European Agency for the Evaluation of Medicines*. As discussed above under point 4.3.6.2, this is an improvement for the evaluation of health hazards as it makes the number of reported cases more manageable thus helping the competent authorities to focus on those cases that are really critical. In addition, this law reduces the workload of pharmaceutical companies to a great extent, which also has financial consequences.

Furthermore, the regulations under sub-section 2, sentence 2b, sub-section 3 and sub-section 6 also came into force in August 2004.

Although the coming into force of the regulations under section 63, sub-section 1 (recording of adverse reactions), sub-section 2, sentence 1 (reporting of serious ADRs which occurred in Germany) and 3 (reporting of drug abuse) and sub-section 4 (scientific evaluation) had been postponed (see above), parts or all of these regulations are identical with the regulations under the old section 29 AMG and therefore, they were already in place with regards to most of the content of the laws⁴⁰. The extended obligations of these regulations, as discussed above, were to come into force at a later point in time.

Even though the coming into force of sub-section 8 had also been postponed, European regulation is directly binding. Sub-section 8 was therefore only a clarification.

The obligation for the submission of PSURs according to section 63, sub-section 5 was also to come into force at a later point in time. This means that the submission of

case reports from other Member States would no longer be required after that as the coming into force of this obligation was connected with the functioning of the European Datamet⁴⁰.

The Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM, communicated on 13 April 2005 that the pharmacovigilance department had started a new electronic system for reports on adverse drug reactions in accordance with the EU requirements. This system opens up the possibility for BfArM to receive electronically, process and pass on reports on adverse drug reactions to the EMEA EudraVigilance Database, for instance⁴¹. According to Prof. Dr. Reinhard Kurth, Head of BfArM, the German regulatory authorities for human medicinal products, BfArM and PEI, herewith belonged to the first regulatory authorities in the EU that had fulfilled to a full extent their part of their contribution to the implementation of the electronic system in the EU. He further stated that BfArM would implement electronic facilities for statistically analysing the available data on ADRs automatically this year as well⁴².

Pursuant to Article 24 of Regulation (EC) No 726/2004, adverse drug reactions have to be transmitted electronically as from 20th November 2005. Pursuant to Article 90 of Regulation (EC) No 726/2004, Article 24 applies from 20 November 2005. From that date adverse drug reactions have to be transmitted⁴³. Therefore, the competent higher federal authorities were under pressure to implement the electronic system for reporting ADRs as soon as possible. On 26 April 2005, the law for amending the provisions for medicinal products, the so-called 12a amendment of the German Drug Law, was promulgated in the Bundesgesetzblatt I No. 23 of 26 April 2005 (pages 1068 - 1069) and came into force on 27 April 2005. All new regulations concerning pharmacovigilance, which had been exempted from coming into force on 6 August 2004 came into force with the 12a amendment of the German Drug Law on 27 April 2005.

5. CHANGES IN THE 14TH AMENDMENT OF THE GERMAN DRUG LAW

5.1 EU Directive 2004/27/EC and 2004/28/EC

As mentioned under point 3 of this thesis, during the second stage of amending the European pharmaceutical legislation, amendments were made to the contents of the most important provisions. In order to take account of scientific and technical progress, the detailed requirements of Annex I to Directive 2001/83/EC on the Community code relating to medicinal products for human were amended. This led to the publication of Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC. Moreover, also because of the experience acquired as a result of the six years operation of marketing authorisation procedures laid down in Regulation (EEC) No 2309/93, Directive 2001/83/EC and in other Community legislation, the Council adopted a package of Community legislation on pharmaceuticals further updating existing rules. "The revised legislation is particularly aimed at 1) responding to innovations, such as the development of new, i.e. biotechnology-derived, substances and gene and cell therapies; 2) enhancing the competitiveness of Europe's pharmaceutical industry, particularly small and medium-sized enterprises in the context of globalisation; 3) ensuring the proper operation of the internal market, in particular in view of the EU's enlargement on 1 May 2004, and; 4) simplifying authorisation procedures and improving transparency"⁴⁴. The review of European pharmaceutical legislation was started optimistically as review 2001. After long negotiations between the EU Commission, the European Parliament and the Member States, the final texts were adopted on 31 March 2004 before the accession of 10 further countries to EU on 1 May 2004 and before the EU parliament elections in

June 2004, which was strategically important^{18,44}. Directive 2004/27/EC on the Community code relating to medicinal products for human use of 31 March 2004 amends Directive 2001/83/EC while Directive 2004/28/EC on the Community code relating to medicinal products for veterinary use of 31 March 2004 amends Directive 2001/82/EC. The amendments touched the following topics in the field of pharmacovigilance:

- Referral procedure according to Article 31 of Directive 2001/83/EC
- Information of the public about drug hazards
- Residence of the qualified person in the EU
- Shortening of the intervals for the submission of PSURs
- The use of international agreed terminology in reporting adverse drug reactions
- Instalment of conciliatory proceedings due to pharmacovigilance data
- Pharmacovigilance Inspections¹⁸

A further Directive of 31 March 2004, Directive 2004/24/EC, also amends Directive 2001/83/EC as regards traditional herbal medicinal products.

The legislation in Directive 2004/27/EC, 2004/28/EC and 2004/24/EC have to be transposed into national law within 18 months after publication. This is to be done in the 14th amendment of the German Drug Law. The draft for the 14th amendment of the German Drug Law was issued on 8 February 2005 (BT-Drs. 15/5316). The hearing for the 14th amendment of the Drug Law took place on 11 May 2005⁴⁵. The first debate took place as planned on 27 May 2005. The final debate was scheduled for 23 September 2005. However, the timelines have changed due to the possible early elections in September 2005 (see point 5.3). Other regulations that will be affected by the 14th amendment of Drug Law include regulations concerning marketing authorisation approval, labelling, patient information leaflets, quality controls and more transparency in the regulatory and surveillance authorities⁵⁵.

5.2 Changes in the field of pharmacovigilance in the drafted 14th amendment of the German Drug Law

5.2.1 Definitions (section 4 AMG) and Enhanced Reporting Responsibilities (section 29, subsection 1a to 1d AMG)

Two new definitions have been added to section 4 of the drafted 14th amendment of the German Drug Law which are related to pharmacovigilance. These are definitions for the risks related to use of a medicinal product and risk-benefit balance. These definitions were introduced to Directive 2001/83/EC through Directive 2004/27/EC and are found in article 1, point 28 and 28a of the amended directive. They are also found under article 1 point 19 and 20 of the amended directive 2001/82/EC.

According to section 4, subsection 27 of the drafted 14th amendment of the German Drug Law, a risk related to the use of a medicinal product is

- a) any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health, for veterinary medicinal products, as regards human or animal health*
- b) any risk of undesirable effects on the environment.*

Risk-benefit balance, according to section 28, is *an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks as defined in subsection 27 point a, for veterinary medicinal products also sub-section 27 point b.*

The wordings for these definitions have been taken over from the amended directives 2001/83/EC and 2001/82/EC. According to the explanatory statement to the drafted

14th amendment of the Drug Law, these definitions have become necessary in view of the new regulations for the approval of generics, the decision for approval of a medicinal product and surveillance. The statement with regards to therapeutic effects applies analogously to diagnostic and prophylactic effects⁴⁶.

A negative risk-benefit balance is now mentioned explicitly in section 25 of the drafted 14th amendment of the Drug Law as being a reason for which the granting of a marketing authorisation may be refused by the competent authorities. This replaces the former wording taken from section AMG: *The competent higher federal authority may only refuse to grant the marketing authorisation if there is reason to suspect that, when used in a manner which is in keeping with its intended purpose, the drug has harmful effects which exceed the bounds considered justifiable in the light of the current state of medical knowledge.* As stated by section 28, any risks of undesirable effects on the environment are only considered for veterinary medicinal products. Members of staff of the Federal Ministry of Health and Social Security⁴⁷ have confirmed this.

The term risk-benefit balance and risk related to the use of a medicinal product has also been inserted into section 29 of the drafted 14th amendment of the Drug Law. Section 29 now contains further obligations, in addition to those under section 63b, which touch the field of pharmacovigilance. According to the new subsection 1a, in addition to the obligations mentioned under section 63b, *the MAH must report immediately all prohibitions and restrictions which have been ordered by the competent authority of every country in which the medicinal product is being sold on the market. He must also report every new information, which may affect the evaluation of the benefits and risks of the medicinal product. When requested for by the competent higher federal authority, he must provide the authority with all data and documents, which prove that the assessment of the risk-benefit balance of the medicinal product should still be positive.* This regulation will help the competent federal authority to continually monitor the safety of the medicinal product.

Furthermore, the new subsection 1d of section 29 of the drafted 14th amendment of the Drug Law states that the MAH must *submit all data in connection with the sales volume of the medicinal product as well as all information available to him in connection with the prescription volume if this is requested by the competent federal authority for reasons of drug safety.* This can also be seen in connection with Section 63b, which states that the MAH must *keep detailed records of ...information about the delivered quantities* of a medicinal product. The competent higher federal authorities usually request for this information from marketing authorisation holders when applying the graduated plan. Up till now, the MAH could supply this information on a voluntary basis. In future the MAH will be forced by law to supply the authorities with information⁴⁷. It will therefore no longer be possible for pharmaceuticals to withhold this information, which might be important for estimating the risk-benefit balance and the risk to public health of a medicinal product. The information which the MAH must submit to the competent higher federal authorities in connection with the launch of a medicinal product on the market, including the pharmaceuticals forms and presentations, and information about temporary and ultimate withdrawal periods of the product from the market according to subsections 1b and 1c, will also help the authorities in the assessment of a drug hazard when a problem has arisen since it will be possible for the authorities to determine retrospectively the periods during which patients were actually exposed to the medicinal products and which pharmaceutical forms and strengths were involved.

The enhanced reporting responsibilities in section 29, subsection 1 to 1d of the drafted 14th amendment of the Drug Law are found in the amended Directive 2001/83/EC, article 23 and 23a as well as amended directive 2001/82/EC, article

27(3) and 27a.

5.2.2 Compassionate Use (section 21, sub-section 2, number 6 AMG)

Section 21, sub-section 2 number 6 of the drafted 14th amendment of the German Drug Law introduces the compassionate use of medicinal products into German national law. Compassionate use was introduced into European legislation during the review 2004 and is found under article 83 of Regulation 726/2004. It is binding law for centrally approved products.

Currently, a medicinal product with a promising therapeutic benefit, but without a marketing authorisation, can only be administered to patients during clinical trials or in a state of emergency according to the current German Drug Law. If the drafted 14th amendment to the Drug Law comes into force as it is, the administration of unapproved medicinal products will be allowed under certain circumstances. Compassionate use means making a medicinal product for which a marketing authorisation has not yet been granted „available for compassionate reasons to a group of patients with chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who can not be treated satisfactorily by an authorised medicinal product“,⁴⁸. The obligations to report adverse drug reactions according to article 24(1) and article 25 of regulation 726/2004 have to be observed for medicinal products under compassionate use⁴⁶. Furthermore, the law states that the details for reporting procedures will be regulated by ordinance according to section 80 of the amended AMG (see point 5.2.8).

5.2.3 Pharmacovigilance system, risk management system and proof of availability of a qualified person (section 22 AMG)

Section 22 of the AMG contains details about the documents that must be submitted together with an application for marketing authorisation. Two new requirements have been added here, which touch the field of pharmacovigilance. This is the transformation of the amended regulation under article 8(3) of the amended Directive 2001/83/EC and article 12 (3) of the amended Directive 2001/82/EC into national law.

I. According to sub-section 2, number 5, the applicant must submit *a detailed description of the pharmacovigilance system and if applicable of the risk management system which the applicant will adopt*. This requirement is based on the requirement found in the ICH Guideline E2E (Pharmacovigilance planning) as well as in the CPMP Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03), which is the implementation of the E2E guideline in the EU. With this law, a legal basis will be established for national rulings for such activities in Germany⁴⁷.

A detailed description of the contents of the guideline cannot be given here, as this would go beyond the scope of this guideline. However, a brief summary is given below:

The CPMP Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03) came into operation in June this year. The guideline is intended to „aid in planning pharmacovigilance activities, especially in preparation for the early post marketing period of a new drug“⁴⁹. It is primarily meant for new chemical entities, biotechnology-derived products, and vaccines but also for established products with significant changes such as new dosage form, new route of administration or a new

manufacturing process for a biotechnology-derived product and for established products that are to be introduced to new populations or in significant new indications or where a new major safety concern has arisen. It states that for products for which no special concerns have arisen, routine pharmacovigilance practices should be sufficient for post-approval safety monitoring without the need for additional actions.

The main focus is on a safety specification and pharmacovigilance plan. It describes a method for „summarising the important identified risks of a drug, important potential risks and important missing information, including the potentially at-risk populations and situations where the product is likely to be used that have not been studied pre-approval. It proposes a structure for a Pharmacovigilance Plan and sets out principles of good practice for the design and conduct of observational studies.“⁴⁹. At the time of approval of a new medicinal product, the knowledge about the risks of this drug is limited to the knowledge gained during pre-clinical and clinical studies⁵⁰. The guideline describes methods of identifying risks, which only become apparent during the marketing phase of the product and strategies of investigating such risks (pharmacovigilance methods).

The Safety Specification is a summary of the important identified and potential risks and it should help the pharmaceutical industry and regulatory authorities to identify any need for specific data collection. The Pharmacovigilance Plan is based on the Safety Specification. It should include a summary of ongoing safety issues (if the plan is a separate document from the Safety Specification), routine pharmacovigilance practices, an action plan for safety issues and a summary of actions to be completed, including milestones.

The key pharmacovigilance methods described in the guideline are:

1. Passive surveillance (spontaneous reports and case series)
2. Stimulated reporting
3. Active surveillance (use of sentinel sites, drug event monitoring, registries)
4. Comparative observational studies (cross-sectional study (survey), case-control study, cohort study)
5. Targeted Clinical Investigations
6. Descriptive studies (natural history of disease, drug utilisation study)

The requirement for the applicant to submit a detailed description of the pharmacovigilance system and if applicable of the risk management system which the applicant will adopt at the time of licence application will force the pharmaceutical industry to deal with the issue of early post approval pharmacovigilance and to actually set up a plan according to the safety requirements of the particular drug, at an early point in time i.e. before the product is approved, to monitor and manage its hazards. This will improve the safety of medicinal products. The early monitoring of the safety of a medicinal product can also help to improve the benefit-risk balance of medicinal products by reducing risks to patients through information feedback to the users of the medicines in a timely manner⁴⁹.

II. According to sub-section 2, number 6, the applicant must prove at the time of licence application *that he has the services of a qualified person who has the necessary means for the realisation of his obligations according to section 63a AMG.*

Currently the commissioner for the graduated plan has to be notified to the local surveillance authority only. With this new regulation, it will become necessary to notify the competent federal higher authority as well. Any changes after that will have to be made via a variation for which fees must be paid⁴⁷.

5.2.4 Information of the public (section 34 AMG)

The heading for the regulations found under section 34 is to be changed from „Promulgations“ to „Information of the Public“. According to the new regulations found under this section, the competent higher federal authority must make available to the public *information concerning the granting of a marketing authorisation together with the SPC and the assessment report together with comments as regards the results of the pharmaceutical, pre-clinical and clinical tests for each indication that has been applied for, after deletion of any information of a commercial confidential nature. Furthermore, in the case of a medicinal product for human use for which the marketing authorisation has been granted subject to a requirement for the applicant to meet certain conditions, these conditions shall be made publicly accessible together with deadlines and dates of fulfilment.* This regulation is a transposition of the regulations found under article 21 (3 and 4) and article 22 of the amended Directive 2001/83/EC as well as article 25 (3 and 4) and article 26 (3) of the amended Directive 2001/82/EC and is also in line with the efforts of the EMEA for more transparency and dissemination of information about medicinal products. According to the EMEA patients should be given access to information about medicinal products so that they can make their own opinions with the objective of encouraging the dialogue between health care professionals and better-informed patients. Access to information about a medicinal product is also the right of every patient⁵¹ and the provision of patients with authoritative information about medicinal products in a language they can easily understand will allow the patient to compare different products (the informed patient)⁵². There is also need to provide better information to health care professionals, especially in the context of pharmacovigilance and urgent safety restrictions⁵¹.

In addition to the above, *decisions to revoke, withdraw or suspend the licence must be made publicly available.* This has been taken over from Directive 2001/83/EC, article 125 and from Directive 2001/82/EC, article 94 (3).

The drafted 14th amendment of the German Drug Law goes on to say that the above mentioned information must be made *publicly available by the competent higher federal authorities on electronic storage media or on site for reference.* This information will probably be made available in the internet⁴⁷, which will facilitate the public to access the information easily.

Currently, BfArM has a system called ASI (Arzneimittel-Schnellinformation), by which it informs the circle of experts about possible drug hazards. By this, experts should be given the opportunity to bring in additional experience to help clarify the suspected drug hazard thereby placing the assessment of the drug hazard on a broader basis of knowledge. In addition to this, ASI informs experts about decisions taken because of drug safety reasons and about new marketing authorisations that may have an outstanding meaning for drug therapy⁵³. This information can be viewed under the BfArM homepage (www.bfarm.de) and is also printed regularly in specific journals such as „Pharmazeutische Industrie“, ECV, Editio Cantor Verlag, Aulendorf, Germany). In addition certain limited information concerning all marketing authorisations, which have been granted in Germany, can be viewed in the database of the German Institute for Medicinal Information (DIMDI). These systems are important sources of information but they are only available to professionals. Systems such as the DIMDI database are not yet available in every country of the EU and the German authorities are quite progressive in this respect. The new law will hopefully lead to further progress in the quick identification of drug hazards. Transparency of information can help physicians to gain helpful and validated information about a drug such as potential benefits, safety and risks, which can be used to make treatment decisions. It may also help the physicians and pharmacists

to make their own opinion about a medicinal product and they would have to rely less on the sales representatives of the pharmaceutical company, whose places of work are dependent on sales figures. Improvement of drug safety will however also be of an advantage for the pharmaceutical industry in the long run.

For patients, information of the public may be useful because their physician does not always advise them about the risks of the drugs they are taking. An informed patient may even indicate risks such as co-medication to his physician and may give his physician useful information about new insights about the safety of a particular drug. In addition, patients may feel more encouraged to report ADRs to their physician or pharmacist or to the pharmaceutical company. However, the information of the public should not preclude physicians and pharmacist from their professional duties and should not interfere in relationships between patients and physicians and patients and pharmacists⁵¹.

In connection to the amended section 34 AMG, it should also be noted that the penalty payments under section 97 of the amended AMG have been extended to include notifications made by the MAH, which have either not been done at all or have not been done in time, or which are not correct or complete and reports of adverse drug reactions which are not correct. These are administrative offences that can be avenged with penalties of up to 25,000 Euro.

5.2.5 Commissioner for the graduated plan (section 63a AMG)

Section 63a of the drafted 14th amendment of the German Drug Law now clearly states that the commissioner for the graduated plan (Stufenplanbeauftragter) must be resident in one of the Member States of the EU (which also means that he must not necessarily be resident in Germany). This corresponds to the amendment made to article 103 of Directive 2001/83/EC and article 74 of Directive 2001/82/EC that „the qualified person shall reside in the community“ and is of particular importance for internationally working pharmaceutical companies.

In addition to this, the commissioner for the graduated plan is now also responsible for *ensuring that upon request from the competent federal authority additional information necessary for the evaluation of the benefits risk balance afforded by a medicinal product, including the own assessment of the commissioner for the graduated plan, is submitted fully and promptly*. This is the transposition of the EU law found under article 103 of Directive 2001/83/EC and article 74 of Directive 2001/82/EC into national law. With this new regulation, the commissioner for the graduated plan will now not only be responsible, by national law, for meeting the obligations to notify in so far as they concern drug risks but he shall now also be responsible for answering requests relating to drug safety of the competent higher federal authorities, especially in relation to the benefit risk balance of a medicinal product. As already mentioned under point 2.3, the commissioner for the graduated plan, unlike the qualified person according to EU regulation, is personally responsible and liable for meeting the obligations set out under section 63a of the AMG.

5.2.6 Reporting responsibilities (section 63b AMG)

5.2.6.1 Reduction of submission intervals for PSURs (sub-section 5)

The maximal interval for submission of PSURs has been reduced from 5 years to 3 years in the 14th drafted amendment of the German Drug Law. This is in accordance with article 104(6) of the amended Directive 2001/83/EC and article 75(5) of the

amended Directive 2001/82/EC and will be done in connection to the new provisions for the renewal of marketing authorisations, which are also to be transposed into national law with the 14th amendment of the drug law. According to the amended section 31 of the AMG, the marketing authorisation may be renewed after 5 years and once renewed, the marketing authorisation shall be valid for an unlimited period, unless the competent higher federal authority asks for an additional five-year renewal on the grounds of preventing a direct or indirect risk of human or animal health. The reduction of the maximum submission interval will ensure a more frequent assessment of the benefit risk balance of a medicinal product because the assessment of the safety of the product during renewal will lapse after the first or second renewal. The reduction of the maximum interval to 3 years should also reduce the risks to public health due to the more frequent assessment.

In addition to this, the new regulation also sets out that the PSUR shall be submitted to the competent higher federal authority, unless otherwise agreed or determined, *immediately upon request or at least every six months after authorisation and until the placing on the market. Furthermore, PSURs must also be submitted immediately upon request or at least every six months during the first two years following the initial placing on the market and once a year for the following two years.* This also makes it clear that PSURs must be submitted for a medicinal product, which is not yet on the market. The short interval of at least 6 months applies in this case.

5.2.6.2 Pharmacovigilance Inspections, (sub-section 5a)

The new sub-section 5a of the drafted 14th amendment of the German Drug Law introduces the legal bases for pharmacovigilance inspections into national German law. It is the transposition of article 111(1d) of the amended directive 2001/83/EC and article 80(1d) of the amended Directive 2001/82/EC. It empowers the competent higher federal authority to inspect pharmaceutical companies that manufacture and market medicinal products or conduct clinical trials in order to control whether the obligations according to section 63b AMG are met. For this purpose, inspectors may enter the premises and facilities of the company to look into documents and demand for information. This is to be done in cooperation with the competent surveillance authority. According to the explanatory statement on the drafted 14th amendment of the German Drug Law, these inspections will be focused especially on individual spontaneous reports of ADEs including deadlines, assessment, follow-up, etc., Periodic Safety Update Reports as well as the organisational structure of the pharmacovigilance system of the company⁴⁶. It goes on to say that because such inspections require a high degree of expertise, the responsibility for these inspections have been placed with the regulatory authorities as they have the necessary information and data about ADR reports from the national database and the EU Eudravigilance database as well as information concerning the status of the submitted PSURs, due to their duties and responsibilities. Furthermore, the documents and data to be inspected are closely related to the marketing authorisation and failure to comply to the requirements laid down in the marketing authorisation can lead to a change in the regulatory status of the medicinal product through direct regulatory measures through the competent regulatory authority⁴⁶.

The explanatory statement says that the costs and the extent of the pharmacovigilance inspections will be determined further during the legislative procedure. It is estimated that about 5 to 10 inspections will be carried out per year if the inspections are only to be carried out due to particular occurrences (in cases where a MAH is suspected of being non-compliant). This will require the position of one scientist and one project attendant in the competent regulatory authority. However, if the inspections are to be carried out on a regular basis, more staff will need to be

employed⁴⁶.

The EMEA issued a position paper on the compliance with pharmacovigilance regulatory obligations in November 2001. It states that pharmacovigilance inspections should ensure that the „MAHs comply with pharmacovigilance regulatory obligations“ and should „facilitate compliance“ and that the results of such an inspection „will be used to help MAHs improve compliance and may also be used as a basis for enforcement of action.“⁵⁴ Pharmacovigilance inspections will further improve compliance of pharmaceutical companies or those conducting clinical trials and thus help to improve the timely assessment of drug hazards.

5.2.6.3 Obligation to Provide Objective Information (sub-section 5b)

A further regulation, which has been transposed into the German national law, is the regulation found under article 104(9) of the amended Directive 2001/83/EC and under article 75(8) of the amended Directive 2001/82/EC, which should ensure that information to the public relating to pharmacovigilance concerns of a medicinal product is presented in an objective way. It says that *the holder of a marketing authorisation may not communicate information relating to pharmacovigilance of his authorised medicinal product without giving prior or simultaneous notification to the competent higher federal authority. He shall ensure that such information is presented objectively and is not misleading.*

5.2.6.4 Reporting Obligations after withdrawal of the marketing authorisation (sub-section 7)

According to the explanatory statement on the drafted 14th amendment of the German Drug Law, the amendment in sub-section 7 is an editorial modification as well as a clarification about the obligations of the MAH after withdrawal of a marketing authorisation. The MAH who has withdrawn his licence must therefore still meet the obligations set out under section 63b, sub-sections 1 to 4, concerning the documentation and reporting of adverse drug reactions. This regulation is new and should ensure that any ADRs which may occur at a later point in time are documented and reported to the competent higher federal authority even if the marketing authorisation no longer exists⁴⁷. This may be important for instance in cases where the product is still in use, even though the marketing authorisation has been withdrawn, because pharmacists still had the medicine on stock or in cases where the MAH applies for a new marketing authorisation at a later point in time. In this case, no information that could influence the safety assessment of the medicinal product would have been lost during the time of no marketing authorisation. However, in order to reduce the workload and financial burden on the MAH, it would be sensible to set a time limit of a few years for reporting ADRs after withdrawal of the marketing authorisation.

5.2.7 Measures to be taken by the competent authorities (section 69 AMG)

The measures that can be taken when *there is reason to suspect, when used in keeping with its designated purpose, a medicinal product has harmful effects which exceed the bounds considered justifiable according to the prevailing standard of scientific knowledge* has been extended to include the suspension of the marketing approval of the product.

5.2.8 Empowerment to issue regulations for procedures (section 80)

The empowerment of the federal ministry to issue regulations for procedures has been expanded to account for the introduction of „compassionate use“ into the German Drug Law. It empowers the federal ministry to issue regulations to govern the duties and responsibilities of the competent higher federal authority, with regards to the cooperation with the European Drug Agency and the Committee for Medicinal Products for Human Use (CHMP)* as well as responsibilities of the physicians, pharmaceutical company and sponsors, including those in connection with obligations for notification, documentation and submission especially of adverse drug reactions. These regulations can also be issued for medicinal products which do not need to be approved through the centralised procedure. The federal ministry can transfer this empowerment to the competent higher federal authority without approval by the parliament (Bundesrat).

5.3 Timetable for Coming into force

As mentioned under point 5.1, the draft for the 14th AMG amendment was issued on 8 February 2005. The hearing on the bill for the 14th AMG amendment (parliament ref. 15/5316), which was originally planned for 2 March 2005 was postponed and took place on 11 May 2005 in the German parliament (Bundestag). The plan is to pass the bill during this legislative period, which may be shortened due to early elections that are most likely to take place in September 2005. The first round in the chamber of parliament representing the federal states (Bundesrat) took place on 27 May 2005. Further debates are scheduled to take place on 16 and 17 June in the German parliament (Bundestag) and on 8 July in the chamber of parliament representing the federal states (Bundesrat)^{45, 71}. The coming into force of the 14th AMG amendment of the German Drug Law has been planned to take place by 30 October 2005 latest, which is the date set out by the EU regulations.

6. DISCUSSION

Each of the changes in the field of pharmacovigilance, which have been introduced into the German Drug law through the 12th and drafted 14th amendment, have already been discussed under point 4 and 5. This discussion is therefore meant to be an overall discussion of the most important changes without going into any further detail concerning each of the changes that have taken place.

Firstly, I would like to point out the difficulties pertaining to achieving a harmonised legislation throughout Europe, even though that is one of the main goals, when transposing European law into national law. This is partly due to the diverse structures and national legislation in the Member States. In addition, history plays an important role, as can be seen in the case of the reporting requirements for serious ADRs caused by medicinal products contaminated with pathogens (see point 4.3.6.2). In the area of pharmacovigilance, the transposition of Directives 2001/83/EC, 2001/82/EC, 2004/27/EC and 2004/28/EC into national law in the 12th and 14th amendment of the German Drug law has not and will most probably not lead to a complete harmonisation of the legislation governing pharmacovigilance with European law. While the reporting obligations for ADEs were rearranged to be in line with the requirement found in Directives 2001/82/EC, some national requirements were added which are likely not to be found in other Member States, such as the requirements for reporting ADRs which were not reported by medical-care

* formerly called CPMP, Committee for Proprietary Medicinal Products

professionals. Another example is the national requirement already mentioned above, to report every serious ADR caused by medicinal products contaminated with pathogens versus suspected serious unexpected transmissions. Nevertheless, the transposition of Directives 2001/83/EC and 2001/82/EC, which are in themselves the result of the merging of a number of EU directives into one consistent directive, and which was already overdue, is an important step toward harmonisation of legislation governing medicinal products in general and pharmacovigilance in particular.

One of the most important achievements in the field of pharmacovigilance, which also had an impact on the regulations governing reporting obligations is the creation of central data-processing network and database management system for the EU, the EudraVigilance system, based at the EMEA. Its purpose is to improve the detection of safety issues by EMEA and regulatory agencies in the EU. In the future, it will be possible to look at trends in statistics in an automated way⁷.

According to a statement of the EMEA concerning the need electronic data transfer found on the EudraVigilance homepage, "the number of suspected serious adverse reaction reports to be managed annually at Community level is estimated at 320.000 whereby the process of preparation, submission, validation and evaluation is very labour intensive and time consuming. In the frame of the ICH M2 activities it has been estimated that the costs of validating essential manual processes for generating paper copies of information represent 50% of the cost of processing the information"⁷. The EudraVigilance system will help to reduce the costs and time involved in the processing of pharmacovigilance data, "achieve uniformity and a high quality of content and format of these data between all partners involved"⁷. It will probably also help to reduce double reporting, since it should be easier to detect double reporting in a computerised system.

A further significant change in the 12th amendment of the German Drug Law is that double reporting of cases which occurred in other Member States is no more required due to the operation of a centralised database into which all Member States report the cases which occurred in their territory. This means that a case, which occurred in a Member State, will now only be reported once by the MAH to the competent authority in the Member State in which the ADR occurred and in the case of an MRP product, to the RMS as well. Since the remaining 24 Member States do no longer report this case as well, this will help the authorities to reduce the workload and finances used for processing and sorting these cases and will lead to more clarity because one part of double reporting is obsolete. In addition, this will also reduce the workload on pharmaceutical companies. In future it might be useful to consider setting up a worldwide database and management system for pharmacovigilance in order to be able to monitor drug safety on a global basis.

Currently, there is an endeavour of the EMEA for more transparency and dissemination of information about medicinal products to medical-care professionals and patients. This will help to improve treatment and the safe use of medicinal products because health-care professionals and patients will have access to more qualified and unbiased information. One of the ways through which this is going to be achieved is by giving health-care professionals and patients access to EudraVigilance. As a prerequisite, the law on providing information to the public will be implemented in the national law with the coming into force of the 14th amendment of the German Drug Law, provided no alterations are made to the drafted amendment in this respect.

However, it is also very important that patients and the general public are made more aware of the processes involved in pharmacovigilance. For instance, patients should be encouraged to ask the medical doctor for the patient information leaflet, if they

have received any medication without one, so that the patient can check any adverse drug reaction that he may experience with the content of the leaflet and also cross check whether he is taking any additional medication that could lead to drug interactions. There should be more encouragement to report observed adverse drug reactions to the physician. This should include ADRs, which are known, unlike the current practice of encouraging patients to report those side effects which have not been mentioned in the patient information leaflet, because this will help correct the frequency evaluation of ADRs.

The improvement of the reporting behaviour of health-care professionals is also inevitable for the enhancement of pharmacovigilance. The rate of reporting of ADRs through medical doctors probably lies around 5 to 10% only². A study conducted in Germany by the European Pharmacovigilance Research Group, which examined the reporting behaviour of two groups of medical doctors – one group picked at random and one group with medical doctors that had reported an ADR between 16 June and 30 November 1997 to the Drug Commission of German Medical Doctors (Arzneimittelkommission der deutschen Ärzteschaft, AkdÄ) showed that of 141 medical doctors picked at random, only 61,3% indicated the reporting of at least one ADR during their professional life. 37.4% reported within the last five years only and 8.3% in the last five years as well as before the last five years. 15.8% did their last report longer than five years ago. 68,2% indicated that they suspected an ADR but did not report. The study also showed that some medical doctors report ADRs to the newspaper “arznei-telegram”, with increasing tendency. The problem about this is that the newspaper, a commercial operation, does not forward these reports to the competent higher federal authorities nor to the AkdÄ, which would in turn forward the reports to the appropriate authority. This means that this information does not become available for the assessment of and defence against drug hazards².

Of all the medical doctors asked, the main reason indicated for not reporting a suspected ADR was that the ADR was a known one (75.6%). This means that this information does not become available for monitoring changes in or for correcting the frequency evaluation regarding particular ADRs. Another reason mentioned for the underreporting was that the medical doctors were not sure that the ADR was definitively caused by the medicinal product (66,3%). However, the reporting form, which appears in the “Deutsches Ärzteblatt”, another newspaper for physicians, indicates that suspected cases of ADRs should be reported as well. One fifth of the medical doctors chosen at random indicated that the system for reporting ADRs was not known to them, 86.7% of all medical doctors asked said that they did not know the criteria for reporting ADRs². These data clearly show that it is not sufficient to reform the regulations governing pharmacovigilance for pharmaceutical companies and competent authorities alone, but that training and regular refreshing of knowledge concerning pharmacovigilance is urgently needed for all health-care professionals for the system to function. Even though the professional statutory order for medical doctors (Berufsordnung) commits all medical doctors to report ADRs, including suspected cases, to the AkdÄ or to BfArM since 1988, this, together with regular appeals to report, is not sufficient. I think that the obligations for reporting ADRs in the German Drug Law should be extended to all health-care professions, as is the case in the current German Drug Law of Austria, section 75, sub-section 1 which states that *medical doctors, dental surgeons, veterinaries, dentists, midwives and, as far as they do not underlie the reporting obligations pursuant to section 75, pharmacists and companies that are authorized pursuant to the trade, commerce and industry regulation act of 1994 to manufacture medicinal products, that are authorized to distribute medicinal products and have pharmacists, are to report*

1. Adverse drug reactions

2. Frequently observed inappropriate use and serious abuse of medicinal products, as well as

3. Quality deficiencies

that have occurred within the country and have become known to them as a result of their occupational activity, immediately to the federal ministry for health and customer protection, according to the requirement of a regulation pursuant to sub-section 4.

However, this would be very difficult to achieve because of the federal structure of the federal republic of Germany, which includes the division of responsibilities between the Federation (Bund) and the federal states known as Laender (Bundesländer). The power of legislation has largely been assigned to the duties of the Federation while to a large extent, administration is the responsibility of the federal states (Laender). The federal states also implement Laender laws as an independent administrative body at federal state level, and they implement federal laws as an administration on behalf of the Federation or in their own responsibility⁶⁹. This is anchored in the Basic Constitutional Law of the Federal Republic of Germany. For instance, Article 30 (Distribution of competence between the Federation and the Länder), states that *“the exercise of governmental powers and the discharge of governmental functions is incumbent on the Laender insofar as this Basic Law does not otherwise prescribe or permit”*, Article 70 (1) and (2) (Legislation of the Federation and the Länder) states that *“(1) The Laender have the power to legislate insofar as this Basic Law does not confer legislative powers on the Federation. (2) The division of competence between the Federation and the Laender is determined by the provisions of this Basic Law concerning exclusive and concurrent legislative powers”* and Article 83 (Distribution of competence between the Federation the Laender), which states that *“The Laender execute Federal laws as matters of their own concern insofar as this Basic Law does not otherwise provide or permit”*, etc⁷⁰.

Legislation governing health-care professions (Heilberufsrecht) is the responsibility of the Laender and not of the Federation. Since, however, the German Drug Law falls under the responsibility of the Federation, it would mean encroaching the authority of the Laender to include an obligation for the health-care professionals to report ADRs in the AMG. This was probably only possible in the case of clinical trials because the federal higher competent authority has the superintendence over clinical trials. The distribution of competence between the Federation and the Laender with respect to the legislation governing health-care professions would have to be changed first before reporting obligations for health-care professionals can be included in the AMG. This would probably be a long and complicated process, if at all it would be possible.

It might also be useful to introduce Good Pharmacovigilance Practice for the field of Pharmacovigilance, similar to other GxP guidelines such as Good Clinical Practice, Good Manufacturing Practice, Good Distributing Practice, etc., as suggested by the authors of the Berliner Deklaration zur Pharmakovigilanz⁶⁷.

Even though many of the changes regarding pharmacovigilance in the 12th and drafted 14th amendment of the German Drug Law as described under points 4 and 5, will probably lead to an improvement in pharmacovigilance and thus the safe use of medicinal products, the new regulations will also add to the burden on the pharmaceutical industry in terms of time and expenses because of an increase in bureaucracy. The new regulations result in more efforts in the maintenance of marketing authorisations under drug safety aspects and within the scope of clinical trials^{65, 66}. Though, pharmaceutical companies are no more required to report cases from other Member States, through the establishment of a central database, other reporting requirements have risen. An example of this is the requirement in the drafted 14th amendment of the German Drug Law, that ADR reporting must be continued even after withdrawal of the marketing authorization. As discussed under

point 5.2.6.4, there may be good reasons for this; however, consideration should be given to setting a time limit in order to relieve the MAH of the workload, which also automatically causes more expenses. In addition, the MAH is now levied with charges for the submission of PSURs.

Generally speaking, more attention should be given to reducing the financial burden on the pharmaceutical industry, taking into account the current difficult economic situation in Germany, while at the same time increasing the quality of pharmacovigilance. In 2003 for instance, pharmaceutical companies were forced to pay 6% of the wholesale dealer's selling price for every pack sold, to the health insurances (Herstellerrabat (Manufacturer's rebate)). The new law, GKV-Modernisierungsgesetz (GMG) of 2004, led and will lead to further financial burdens on the pharmaceutical industry, especially for middle-sized companies, through measures such as the increase of the rebate to 16% in 2004 (which led to savings of around 1.7 billion Euro - 100 million Euro more than had been designated to be saved by this measure) and the extension of fixed pricing to affect medicinal products under patent⁶⁵. The new regulations in the 12th and 14th amendments of the Drug Law in general and those for pharmacovigilance in particular, will lead to further financial burdens on the industry and this may lead to a loss of attractiveness for Germany as a location for pharmaceutical industry and clinical research. More intensive discussions between legislators and the pharmaceutical industry would certainly be useful.

The laws governing pharmacovigilance are widely ramified. Issuing regulations that are easier to understand to enable good functioning of the system should be considered.

Pharmacovigilance inspections will certainly lead to a higher quality in pharmacovigilance because the abidance to laws governing pharmacovigilance will be checked and controlled to a greater extent than before. However, it would be useful if competent authorities would provide free training on pharmacovigilance for pharmaceutical companies in several towns in the country. This would avoid additional expenses on the side of the industry and could justify the fees charged for the submission of PSURs (see point 4.3.2). However, the distribution of competence between the Federation and the federal states (Laender) may also pose a problem here for the transposition of the EU law into national law because surveillance is the responsibility of the Laender and not of the Federation (in this case the competent higher federal authority). It remains to be seen how the transposition of this law into national law will be achieved.

Furthermore, it would be very useful to introduce an international medical terminology designed to support the classification and standardised communication of medical information, such as MedDRA (Medical Dictionary for Regulatory Activities), free of charge, because access to MedDRA is very expensive and would currently be more than middle-sized and small companies can probably afford.

7. CONCLUSION AND OUTLOOK

The 12th amendment of the German Drug Law has lead and the 14th amendment of the German Drug Law will lead to many changes in the field of pharmacovigilance. Many of these changes are useful and were actually overdue. At the same time the burden in terms of time and finances have and will increase on pharmaceutical companies and probably also on regulatory authorities because of the increase in bureaucracy. However, efforts must continuously be made to increase the quality of pharmacovigilance and to keep pace with scientific development and globalisation in

order to protect human health, animal health and the environment. The results of the amendments to the German Drug Law will be seen within the next few years and then it will probably be time to update or amend the law again according to the experience gathered. However, despite the large and important benefits of medicinal products for human beings, they will continue to present a risk as well, regardless of how good the regulations and how sophisticated the system for pharmacovigilance is.

*“Ideals are like stars:
One cannot reach them
But one can be geared to them”*

Free translation from the original:

*“Ideale sind wie Sterne:
Man kann sie nicht erreichen,
aber man kann sich nach Ihnen orientieren”
(Carl Schurz)*

8. SUMMARY

The rapid development in science and globalisation has led to an increase of medicinal products on the market. While this is a positive development for patients on the one hand, it also poses more risks of drug hazards for patients on the other hand. The purpose of Pharmacovigilance is to detect, assess, understand and prevent adverse effects or any other possible drug-related problems.

Pharmacovigilance is governed by regulations of the European Union, which are either directly binding or have to be transposed into national legislation within a given timeframe, and by national legislation.

The purpose of this thesis is to describe the changes, which have been introduced into the 12th amendment of the German Drug Law in the field of pharmacovigilance as a result of the transposition of EU regulation and for other reasons such as the experience made with the old law. The EU regulations include Directive 2001/83/EG (relating to medicinal products for human use), Directive 2001/82/EG (relating to veterinary medicinal products), Directive 2001/20/EG (relating to Good Clinical Practice) and Directive 2002/98/EG (setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components). Besides changes in the field of clinical studies, the changes related to pharmacovigilance belong to the major changes, which were introduced into the 12th amendment of the German Drug Law. In addition, this thesis describes the changes in the field of pharmacovigilance in the drafted 14th amendment of the German Drug Law, in which Directive 2004/27/EC and directive 2004/28/EC (review of pharmaceutical legislation in 2004), will be transposed into national law. The 12th amendment of the German Drug Law came into force on 6 August 2004, while the 14th amendment of the German Drug Law has been planned to come into force latest by 30 October 2005, which is the date set out by the EU regulations.

One of the major changes to pharmacovigilance is the implementation of a central database for the collection and management of pharmacovigilance data, based at EMEA, which has also led to the amendment of the obligations for reporting adverse drug reactions.

Another major change has been the introduction of a new section, section 63b, under chapter 10 „Observation, Collection and Evaluation of Drug Hazards“ of the German Drug Law. The obligations for recording and reporting adverse drug reactions are now arranged under this section and have been deleted from section 29 AMG.

A further major change which was introduced to the 12th amendment of the German Drug Law was the revision of the regulations governing clinical studies and adaptation to the contents of the GCP Directive 2001/20/EC. For the first time, a separate regulation has been issued in Germany with detailed regulations for the conduct of clinical trials. This regulation, which is called “Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen” (GCP-Verordnung - GCP-V) also contains detailed regulations concerning the obligations of the investigator, the sponsor and the competent higher federal authority to report adverse drug reactions which have occurred during a clinical trial.

A further change in the Drug Law is the addition of a law by which the competent higher federal authorities are authorised to levy charges for activities carried out relating to pharmacovigilance.

Furthermore, the submission of PSURs was introduced into the German Drug Law

within its 12th amendment, with a maximal interval for submission of 5 years. This is proposed to be reduced to 3 years with the 14th amendment of the German Drug Law and will be done in connection to the new provisions for the renewal of marketing authorisations, which are also to be transposed into national law with the 14th amendment of the drug Law. The marketing authorisation will then be renewed after 5 years and once renewed, the marketing authorisation will be valid for an unlimited period, unless the competent higher federal authority asks for an additional five-year renewal on the grounds of preventing a direct or indirect risk of human or animal health. The reduction of the maximum submission interval will ensure a more frequent assessment of the benefit risk balance of a medicinal product because the assessment of the safety of the product during renewal will lapse after the first or second renewal. The reduction of the maximum interval to 3 years should also reduce the risks to public health due to the more frequent assessment.

The legal basis for pharmacovigilance inspections has also been planned to be implemented with the 14th amendment of the German Drug Law.

Even though many of the changes regarding pharmacovigilance in the 12th and 14th amendment of the German Drug Law will probably lead to an improvement in pharmacovigilance and thus in the safe use of medicinal products and were actually overdue, the new regulations will also add to the burden on the pharmaceutical industry in terms of time and expenses because of an increase in bureaucracy. The new regulations result in more efforts in the maintenance of marketing authorisations under drug safety aspects and within the scope of clinical trials.

In addition to putting regulations in place for increasing the quality of pharmacovigilance, there should be more training of health-care professionals and increasing the awareness of the public concerning the pharmacovigilance system.

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10. ANNEX

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

München, den 13.06.2005

Stephanie Iquoeyen Lemke