The legal standards for the radioactive or non radioactive drugs research and approval in the European Community and in Germany after the thalidomide catastrophe*

Abstract

The drug thalidomide was contained in the blockbuster Contergan®, which has been used as a non-prescription sedative drug and a potent treatment for occurring morning sickness in pregnant women during the 1950s and the early 1960s. This therapeutic use has led to one of the most prominent disasters in the history of drug development due to peripheral neuritis and malformations, e.g. phocomelia, in babies whose mothers had taken thalidomide within their pregnancies. Moreover, this catastrophe initiated a change of paradigm in Germany as well as in Europe with regard to drug safety and the regulatory setting. This article describes the history of the use of thalidomide and the regulatory framework of drug approval at that time as well as changes after the Contergan® disaster including considerations to radiopharmaceuticals. Additionally, aspects of drug safety in the different development phases of pharmaceuticals as well as radiopharmaceuticals, i.e. pre-clinical and clinical phases, are characterised. However, many drugs have been withdrawn from the market after approval due to changes with regard of their risk-benefit balance after the occurrence of adverse drug reactions. Thus, pharmacovigilance activities are also mentioned in this review article. Last, obstacles and future perspectives in the arena of drug research and development also considering the use of radiopharmaceuticals are delineated.

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Introduction

The issue of this work is to describe the historical background of the Contergan® (a thalidomide containing drug) disaster in the context of the existing regulatory framework at that time. Pre-clinical and clinical phases necessary for radioactive or non radioactive drug research will be described in detail. Furthermore, the undertaken activities which tend to ensure drug safety, in the different development stages of medicinal products as well as after market authorisation, will be discussed in general as well as in particular with regard to the special population of pregnant women and women with childbearing potential, amongst others. Moreover, currently occurring challenges and future perspectives will be described.

Historical background of the use of thalidomide

The drug thalidomide, a synthetic glutamic acid derivate, was synthesised in 1954 by Wilhelm Kunz, a pharmacist working at Chemie Grünenthal in Stolberg near Aachen/Germany [1]. The rationale for the drug development was an intended use for the treatment of epilepsy, but the drug lacked to show efficacy in this indication [2]. The results from animal toxicology studies in rodents were remarkable because the drug had been well tolerated and had not shown a lethal effect even in high doses, which has led to the conclusion that thalidomide was nontoxic and safe [3, 4]. These results had been confirmed by several clinical trials. Thus, the drug was introduced by Chemie Grünenthal as a safe non-barbiturate sedative and hypnotic drug and registered in June 1957 in Nordrhein-Westfalen, Germany. One month later, the manufacturing of thalidomide containing drug was approved by the local authority, the "Gesundheitsabteilung des Nordrhein-Westfälischen Innenministeriums" [4]. Additional to the above mentioned indication, Contergan® was very popular for the treatment of occurring morning sickness during pregnancy [5]. In the time from 1957 until 1961 thalidomide containing drugs were on the market in 46 countries and under 37 trade names [3].

Contergan® was the most sold hypnotic drug in Germany in the year 1959 and account-

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ed for the half transaction volume of Chemie Grünenthal in the year 1960 [4] with a sales amount of 14.6 tons [5]. In the USA the approval for Kevadon, a thalidomide containing product was denied by the U.S. Food and Drug Administration (FDA) in 1960 because of concerns regarding drug safety, primarily due to the suspicion that thalidomid could cause peripheral neuritis [3, 4]. In May 1961 Contergan® was changed to a prescription drug [4].

In the meantime thalidomide already had been considered to reveal a teratogenic potential [4]. In December 1961 Chemie Grünenthal withdrew Contergan® from the market. The exact number of children who suffered from thalidomide induced malformations is unknown. Estimations range from about 8000 to 12.000 worldwide. The number of patients who suffered from-in part irreversible-neuropathy is estimated at about 40.000 [3].

In 1965 thalidomide already experienced a renaissance as it was successfully used for the treatment of erythema nodosum leprosum (ENL), a painful dermatologic complication of leprosy and is approved in the USA for the chronic treatment of ENL since 1998 [6]. Further, thalidomide has been and is currently investigated because of its various properties for the treatment of several other dermatological, neurological, inflammatory diseases and in particular of malignant diseases [7, 8] and has a market authorisation approved by the FDA since 2006 [2] as well as by the European Medicines Agency (EMEA) since 2008 [9] for the treatment of multiple myeloma in combination treatment with melphalan and prednisone/dexamethasone. Moreover several derivates (so called immuno-modulatory substances, IMiDs®), e.g. modifications of the thalidomide molecule, have been synthesised and screened for potential applications [1].

Development of the regulatory framework. National regulatory activities and medicinal product approval in the European Community and in Germany

Medicinal products had exclusively been produced by physicians until the 13th century and after this time by pharmacists in retail pharmacies. In the 19th century the first pharmaceutical companies arised, e.g. Merck in Darmstadt/Germany, Hoffman La Roche in Basel/Switzerland and others. By the formation of the chemical industry in Europe about 1860 the pharmaceutical industry also begun to arise, and today medicinal products are mainly produced by pharmaceutical companies and only in exceptions by the pharmacies [10].

All member-states of the European Community have a national system of regulation for pharmaceutical product approval which is in strongly influenced by European legislation. The European Commission (EC) can pass regulations which are generally binding as well as directives which have to be implemented in national law within two years. Recent important directives such as the "Clinical Trial Directive", 2001/20/EC, requiring the implementation of the Good Clinical Practice principles (GCP) in the field of clinical research [11] or directive 2001/83/EC, which deals with the content of national procedures of drug approval and pharmacovigilance requirements, amongst others [12], have been released by the EC. Important regulations are No 2309/93 [13] and EC/726/2004 [14], the last stipulates the centralised approval procedure, which is compulsory for specific medicinal products, e.g. for gene therapy, somatic cell therapy and human tissue engineering, amongst others. Moreover, the European Agency for the Evaluation of Medicinal Products was renamed into European Medicines Agency (EMEA) representing the supranational competent authority within Europe. The above mentioned directive 2001/83/EC also applies for radiopharmaceuticals [12]. However, beside the marketing approval by the competent authorities, specific radiation protection regulations in each member state have to be considered, respectively.

The first German national drug law (GDL) was developed and came into force in August 1961 [15]. After the outcome of the Contergan® disaster, in 1964 changes in the GDL with corrective actions regarding drug safety were established, e.g. data of pharmacological-toxicological studies as well as of analytical testing were required prior to registration. Further data of clinical trials were to be provided. All new drugs were automatically prescription drugs for a time span of three years [16]. After 1978 it was obligatory to provide data for quality, safety and efficacy of medicinal products to the competent authority as precondition for obtaining an approval. The formal registration procedure was substituted by an approval procedure. Amongst others, further important aspects which were considered are the liability provisions for the manufacturer in case of health damages caused by a pharmaceutical and not at least the requirements in the area of pharmacovigilance, with the aim of monitoring medicinal product associated risks [17]. Fifteen amendments for improving this law have taken place. The last one recently came into effect in September 2009.

Aspects of drug safety during drug development until market authorisation

Pre-clinical development phase

The pre-clinical drug development phase comprises the assessment of pharmacodynamic and pharmacokinetic properties. as well as studies of single dose and repeated dose toxicity, reproductive toxicity, genotoxicity, carcinogenicity, immunotoxicity, local tolerance and environmental risk assessment of radioactive and non-radioactive drugs. Pre-clinical radioactive studies have to be authorized according to local, country-specific regulations. The aim of this developmental stage is to address potential safety issues prior to the start of the clinical development phase including the collection of important data with regard to dose estimations for first trials in humans. These investigations are conducted in vivo in animals (rodents and non-rodents), as well as in-vitro by using cell and tissue assays [18]. The selection of appropriate animal models is crucial and has to be relevant to humans with regard to pharmacodynamic, pharmacokinetic and toxicity mechanisms [19]. *Commonly,*

tests are performed in at least one rodent, generally mouse or rat, and in one non-rodent species, e.g. rabbit or dog. Nevertheless, sometimes the use of non-human primate models can be required due to physiological similarities, e.g. in the setting of preclinical development of monoclonal antibodies [20].

Due to several factors, the results of animal studies can not always be applied for estimating the risks for human exposure. For example, differences in sensitivity between test animals and humans to specific enzyme inhibition or induction as well as distinctions in metabolism/biotransformation of drugs, e.g. occurrence of different metabolites in specific species, can be a reason for false results [21, 22]. Even if a unique human metabolite is synthesised and administered exogenously to test animals, differences in pharmacokinetics in comparison with humans (i.e. in absorption, distribution, metabolism and excretion) may lead to a decreased predictive value of the test results [23]. Moreover, sex-differences have been observed which can lead to different outcomes in toxicity testing. Toxic effects which are caused by a drug at high doses in animals, will not necessarily lead to the same effects in humans at therapeutic doses [21]. Nevertheless, it is essential to apply toxicokinetic parameters in order to evaluate systemic exposure in relation to the administered dose to test animals [24].

Clinical phase

When a pharmaceutical product has successfully finished the pre-clinical development phase and the risk-benefit balance is considered as adequate for testing the drug in humans, it enters the clinical phase.

All clinical trials of radiopharmaceuticals and non-radiopharmaceuticals, respectively, have to be conducted in compliance with the principles of Good Clinical Practice (GCP) according to the European Clinical Trial Directive [14]. These principles are described in the Note for Guidance on Good Clinical Practice by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), topic E (efficacy), no. 6, which is an internationally accepted scientific standard for designing, conducting, recording and reporting clinical trials. Good Clinical Practice has its origins in the Declaration of Helsinki which is common standard for safeguarding the rights and the well-being of subjects participating in clinical trials [25]. In addition, several other ICH guidelines reflect the current standards in the area of clinical research, e.g. ICH topic E3 - Structure and Content of Clinical Study Reports [26] or ICH topic E2A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting [27], amongst many others.

One can classify clinical studies either by the phase of the development stage (Phase I-most common type: human pharmacology study; Phase II- most typical type: therapeutic exploratory study; Phase III - most common: therapeutic confirmatory and Phase IV-most typical: therapeutic use) or by the study objectives. The latter possibility is preferred as one type of study can occur in several development stages. The different study types are briefly described in Table 1 adopted from the ICH Note for Guidance on general considerations for clinical trials together with examples in order to provide an overview of required information by the authorities for the marketing application of a medicinal product.

The types human pharmacology study, therapeutic exploratory and confirmatory studies are usually parts of the clinical development programmes prior to application for market approval. However, in exemptions the authority can demand further data from therapeutic use in case of concerns with regard to safety or efficacy of a medicinal product [28].

Table 1. *An approach to classifying clinical studies according to objective (adapted from [28]*

Type of study	Objectives of study	Study examples
Human pharmacology	Assess tolerance Define/describe PK[1] and PD[2] Explore drug metabolism and drug interactions Estimate activity	Dose-tolerance studies Single and multiple dose PK and/or PD studies Drug interaction studies
Therapeutic exploratory	Explore use for the targeted indication Estimate dosage for subsequent studies Provide basis for confirmatory study design, endpoints, methodologies	Earliest trials of relatively short duration in well- defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures Dose-response exploration studies
Therapeutic confirmatory	Demonstrate/confirm efficacy Establish safety profile Provide an adequate basis for assessing the benefit/risk relationship to support licensing Establish dose-response relationship	Adequate, and well controlled studies to establish efficacy Randomised parallel dose response studies Clinical safety studies Studies of mortality/ morbidity outcomes Large simple trials Comparative studies
Therapeutic use	Refine understanding of benefit/risk relationship in general or special populations and/or environments Identify less common adverse reactions Refine dosing recommendation	Comparative effectiveness studies Studies of mortality/morbidity outcomes Studies of additional endpoints Large simple trials Pharmacoeconomic studies

[1]Pharmacokinetics [2]Pharmacodynamics

A detailed discussion of the different study types would exceed the limits of this work but it can be summarized that the clinical development program of a pharmaceutical has to be designed in order to examine essential information regarding safety, e.g. mortality, morbidity, adverse events related to the investigational medicinal product, drug interactions, and efficacy in comparison to standard therapies and/or placebo and the resulting study reports are accurately reviewed by the authorities within the approval procedure.

Radiopharmaceuticals and GCP

Unlike a non-radioactive drug, radiopharmaceuticals consist of a drug part and a radionuclide part. All pharmaceuticals must be prepared under good manufacturing practice (GMP) conditions, but special care has to be taken into account for the radiopharmaceuticals comprising clean room environtmental requirements, specially trained personnel requirements, quality control, dosimetry, and nuclear medicine equipment. In addition, country-specific radiation protection laws and guidelines have to be addressed both in clinical use and especially in the research setting. In Germany the Bundesamt für Strahlenschutz (BfS) is the competent authority for approval of clinical research with radiopharmaceuticals.

The challenge and rationale of pharmacovigilance

Many drugs have been withdrawn from the market after the occurrence of serious unexpected adverse drug reactions. Well known examples are the cyclooxygenase-II-inhibitors, most notably rofecoxib (Vioxx®), which had been associated with an increased incidence of cardiovascular complications [29].

Drug related risks can often not be detected during the clinical development phase as the number of patients treated under the conditions of clinical trials is usually too small and the duration of drug exposure insufficiently long for detecting rarely occurring adverse events [30, 31] or because these adverse events show a long latency [29].

In addition, the results of randomised clinical trials lack when they are applied on patients in clinical practice because multiple factors intervene, e.g. co-morbidity, other concomitant drugs and therapies, drug to drug, or drug to food interactions, amongst others. Pharmacovigilance, according to the World Health Organisation (WHO), is defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem" [29, 30].

According to Directive 2001/83/EC [12], implementation of pharmacovigilance systems is required in each EU member state on a national level. In Germany, according to §63 of the German Drug Law [17], an administrative regulation called "Stufenplan" governs the collection and reporting of suspected adverse drug reactions and assigns responsibilities to the local as well as to the national authorities, to the sponsors/Marketing Authorization Holders (MAH) and the health care professionals, respectively. Supranational within the European Community, according to Regulation EC/726/2004, the EMEA is responsible for coordinating pharmacovigilance activities for all member states.

The marketing authorisation holders of medicinal products have to designate a qualified person pharmacovigilance (QPPV) who resides in the EU and is responsible for all issues related to the collection, recording and reporting of information regarding the risk benefit evaluation of an approved medicinal product [32]. According to Eudralex Volume 9A, a guideline which was developed by the EC in 2008 and to the stipulations of the above mentioned directive and regulation, a comprehensive description of the established pharmacovigilance system, e.g. written procedures for expedited reporting, used databases including validation, availability of QPPV, amongst many other details, and if necessary one of the planned risk management system has to be included in any application for medicinal product approval [33].

Post marketing surveillance

A sponsor (an individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial) [25] or a MAH is generally required to maintain a system which contains detailed records of all suspected adverse drug reactions reported worldwide in the context of clinical trials as well as after marketing authorisation [32]. These have to be reported in defined regular intervals, in so called periodic safety update reports (PSUR) to the authorities, as well as in cases of suspected unexpected serious adverse reactions (SUSAR) by expedited reporting within 15 days or in case of death within 7 days, respectively. Furthermore, PSURs have to be submitted to the authorities immediately on request [12, 14]. Spontaneous reporting is the primary method of collection post-marketing information of drug safety. Criticism about spontaneous reporting addresses the tendency of selective as well as underreporting because of occurring selection bias by the healthcare providers [29].

Risk management

If requested, applications for marketing authorisation must include a detailed description of a risk management system which will be introduced by the MAH. This information has to be submitted in the form of an EU Risk Management Plan (EU-RMP) within the application documents to the authority [15, 17].

Components of an EU-RMP are a safety specification, which should be a summary of the important identified risks of a medicinal product, and a pharmacovigilance plan, which is based on the safety specification as recommended by the ICH E2E topic Pharmacovigilance Planning [33] as well as an analysis of the need of risk minimisation activities [32].

Examples for applications which have to include an EU-RMP are new chemical entity containing medicinal products, biosimilars and amongst others, generic medicinal products where safety concerns are known for the reference products which necessitate risk minimisation activities. These activities are to be submitted in a risk minimisation plan. Risk minimisation activities can be divided in those which achieve risk minimisation by providing information and education and in others which control the use of a drug. Thus, provision of infor-

mation, educational material, legal status of a medicinal product, restricted access programmes and others can contribute to a decreased risk [31]. Excellent examples of risk minimisation activities are the programmes "System for thalidomide education prescribing and safety" (S.T.E.P.S.) and the adaption of Pharmion "Pharmion Risk Management Programme" (PRMP) implemented by Celgene and Phamion, two companies which distribute thalidomide containing products. These programmes comprise educational activities, e.g. informed consent procedure, information about risks, as well as restrictive activities, e.g. registration of both, physician and patient, conduct of pregnancy tests and restricted availability only in registered pharmacies, amongst others. Thus, high-level information about potential teratogenic effects and controlled access of the drug shall prevent any foetal exposure which could lead to malformations in newborn children [34].

Post approval research

Post authorisation safety studies (PASS) are defined as "a pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product" [12]. The competent authorities can require PASS as a commitment of the MAH at the time of marketing approval or in the post approval phase as an integral part of the EU-RMP [31].

Risk assessment of drug use in pregnancy and considerations for special populations

General considerations

In particular, pregnant women do represent a kind of "orphan population" with regard to the use of medicinal products due to lacking information of drug safety in pregnancy. Preclinical toxicology data are not completely predictive for humans, in particular with regard to pregnant women and foetal exposure [35]. However, at the time of marketing approval, these data are virtually the only source of information regarding the evaluation of reproductive risk for a medicinal product. Pregnant women must be excluded from participation in clinical trials because of ethical considerations, i.e. treatment with drugs which can affect the well being of the mother as well as the foetus is not ethically justifiable and clinical studies with radiopharmaceuticals in pregnant subjects should be avoided in any means. Exceptionally, clinical trials with products which are specifically intended for use in pregnancy, i.e. folinic acid containing products, can be conducted in pregnant women. Thus, women with childbearing potential who participate in clinical trials generally have to use effective contraception methods [36]. Most medicinal products are contraindicated per label for use during pregnancy. However, pregnant women often coercively need medication in case of existing diseases, e.g. epilepsy, asthma, infectious diseases, diabetes, thyroid diseases, amongst others. In other cases women are not aware of their pregnancies at the time of drug exposure. The use of medicinal products during pregnancy often happens as "off-label-use", which means that a prescribed product is not approved for the particular disease or population [37].

There is a need for accurate and evaluable information about gestational timing of pregnancy and medicinal product administration. Furthermore, the dose as well as the dosing intervals which cause adverse effects leading to harm of the foetus or the child have to be known, in order to make estimations of the dose-response relationship possible, i.e. parameters like the "no observed adverse effect level" (NOAEL) or the "lowest observed adverse effect level" (LOAEL).

These parameters have to be regarded with caution due to the fact that often remarkable pharmacokinetic inter-individual variances can occur, which means that the same exposure of a drug can lead to differences in absorption, distribution, metabolism and excretion of the active ingredient. The consequence can be increased or decreased plasma levels of active drugs or metabolites, respectively.

However, information about NOAEL and LOAEL of a drug can give some evidence about dose-response relationships [38].

Additional to pregnant women, children and the elderly are also populations, in which age dependant variabilities with regard to pharmacokinetics of administered drugs can lead to changes in adverse drug reaction patterns [39].

Sources of information. Pre-authorisation studies

In clinical trials which include women with childbearing potential, unintentional pregnancies may occur. In such cases, data of exposure and outcome of the pregnancies should be collected. Furthermore, in cases of necessary treatments due to underlying diseases in pregnant women, the characterisation of pharmacokinetic variables as well as the outcome of pregnancies should be regularly reported [36].

Post-authorisation data: Spontaneous reports of pregnancy exposure

Spontaneous reports are the most common source of post-authorisation data about exposure to medicinal products during pregnancy and represent a necessary tool. MAH are required to follow up all reports from health care professional, about the use of their products during pregnancy [36].

Several registries are used in order to accumulate exposure and outcome data for both, mother and foetus. Birth defect registries are population based for children born with congenital abnormalities and represent the basis for research on birth defects. Pregnancy registries are tools for the assessment of drug safety during pregnancy [36]. Teratology Information Services (TIS) are advisory centres and are commonly organised in collaborations, e.g. European Network of Teratology Information Services (ENTIS) or Organization of Teratology Information Services (OTIS) in the USA, respectively. Additionally, these centres are active in recruitment of pregnant women who can be included in pregnancy registries and conduct pharmacoepidemiological research.

Data provided by registries can be combined/linked with each other in order to investigate special causal relations in

subsequent times [30], e.g. cross-linking exposure data with later available information.

A harmonisation of standard formats for electronic spontaneous reports is highly recommended [40], as it facilitates record-linking and the use of provided data in an increased number of registries and thus, allows better pharmacoepidemiological research.

Obstacles in pharmaceutical research and development and various related initiatives

The comprehensive legal stipulations and guidances in the area of drug development and approval tend to ensure safe and effective medicinal products for disease treatment. Innovations, i.e. drugs addressing new targets or have an advanced risk-benefit profile in comparison with already available products, should be developed. However, many pharmaceutical development programmes are aborted, often in late clinical phases, due to lacking efficacy or occurring toxicity issues [41-43]. A recent example beside the prominent TeGenero disaster is the attrition of the drug torcetrapib, an inhibitior of cholesteryl ester transfer protein (CETP), which has led to acute increases of blood pressure and following deaths within the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial, a phase-III trial comparing the efficacy of torcetrapib with torcetrapib in addition to atorvastatin [44].

Thus, there is a need to use the increased knowledge and advances in pharmacokinetics, genomics, functional imaging techniques, and others for the validation and implementation of new biomarkers as surrogate end-points [41]. The U.S. Food and Drug Administration (FDA) proactively released a report with the title "Innovation or Stagnation, Challenge and Opportunity on the Critical Path to New Medical Products" in the year 2004 and later amended the so called "Critical Path Opportunity List" with planned activities in six broad areas: a) Biomarker development, b) Streamlining clinical trials, c) Bioinformatics, d) Manufacturing, e) Antibiotics and countermeasures to combat infection, f) Developing therapies for children and adolescents [42].

Analogously to the U.S. approach, in Europe the publication "Joint Undertaking for the Implementation of the Joint Technology Initiative on Innovative Medicines" was released in the Official Journal in February 2008 and was initiated by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the EC with the aim to encourage safety and efficacy of medicinal products as well as knowledge management and education in research and development [45].

As a consequence, many initiatives have been established in collaborations by several stakeholders in research and development, e.g. pharmaceutical industry, university research groups, authorities with the aim to develop new ideas in research and development, reducing costs and resources while improving the predictability of risk-benefit-balance of a product in early phases [46].

The integration of functional imaging techniques as well as radiopharmaceutical therapies in drug development, in particular in early phases, is called Clinical Technologies Implementation (CTI) and can contribute to a better understanding of drug characteristics and safety patterns. The idea is a more comprehensive investigation of a drug in this early stage of development programmes in contrast to late clinical phases. Thus, a more efficient input of resources regarding time and money can be achieved [47].

In reviewing the above the legal framework of drug regulation and approval has been transformed until today in a consequent manner.

Drug development with its several phases tends to accumulate information about the quality, efficacy and safety of a product before approval by the authorities in order to prevent the incidence of drug catastrophes as the Contergan® example in the past. Moreover, a comprehensive pharmacovigilance system targets to provide safety and quality related issues of medicinal products after market authorisation. It is common knowledge that the content of information about a drug is incomplete at the time of approval.

Particular populations such as pregnant women as well as children and the elderly have to be considered more with regard to inclusion in clinical research. Thus, comprehensive data of drug exposure will be available with the aim of a better predictability of drug safety in specific groups of the population. For this purpose, if a participation in clinical trials is not feasible due to ethical considerations, pharmacoepidemiological research has to be applied.

Unfortunately, the pharmaceutical industry sometimes lacks to transform advances in research into new, innovative and safe products. The reasons for that are the insufficiency and/or the tentative acceptance of new, validated biomarkers and surrogate parameters. In the USA as well as in Europe private and public initiatives in collaboration are established, which aim to develop new ideas in research and development which are able to reduce costs and resources while improving the predictability of risk-benefit-balance of a product in early phases.

The enhanced use of radiopharmaceuticals in the area of Clinical Technologies Implementation (CTI), e.g. functional imaging in proof-of-concept as well as in dose finding studies, can lead efficiently to a comprehensive characterisation of drugs including radiopharmaceuticals in early phases.

In conclusion, the national german as well as the supranational setting for drug approval has rapidly changed after the thalidomide disaster and today drug safety is a crucial aspect in all development phases, i.e. pre-clinical and clinical phase, of a medicinal product including radiopharmaceuticals as well as after the marketing authorisation in the challenging area of pharmacovigilance. Furthermore, special populations as pregnant women, children and the elderly have to be considered in this context. However, there are obstacles in the area of research and development which may lead to stagnation in the development of innovative medicinal products and which have been addressed by initiatives in the USA as well as in Europe.

Bibliography

1. Holzgrabe, U. Ein altes Schlafmittel als Cancerostatikum. Die neue Karriere des Thalidomids. *Pham. Unserer Zeit* 2007; 36: 446-449.
2. Melchert M, List A. The thalidomide saga. *Int J Biochem Cell Biol* 2007; 39: 1489-1499.
3. Silverman WA. The Schizophrenic Career of a "Monster Drug". *Pediatrics* 2002; 110: 404-406.
4. Maio G. Zur Geschichte der Contergan-Katastrophe im Lichte der Arzneimittelgesetzgebung. *Dtsch Med Wochenschr* 2001; 126: 1183-1186.
5. von Moos R, Stolz R, Cerny T, Gillessen S. Thalidomide: From tragedy to promise. *Swiss Med Wkly* 2003; 133: 77-87.
6. Calabrese L, Fleischer AB. Thalidomide: Current and Potential Clinical Applications. *Am J Med* 2000; 108: 487-495.
7. Teo SK, Stirling DI, Zeldis JB. Thalidomide as a novel therapeutic agent: new uses for an old product. *Drug Discov Today* 2005; 10: 107-114.
8. Franks ME, Macpherson GR, Figg WD. Thalidomide. *Lancet* 2004: 1802-1811.
9. 9. EMEA. Europäischer öffentlicher Beurteilungsbericht (EPAR) Thalidomide Celgene (EMEA/H/C/823).2009; downloaded on 21.11.2009 at http://www.emea.europa.eu/humandocs/PDFs/EPAR/thalidomidecelgene/H-823-de1.pdf
10. Fricke FU, Schöffski O. Die Pharmazeutische Industrie und der Arzneimittelmarkt. In: Schöffski O, Fricke FU, Guminski W. *Pharmabetriebslehre*. 2nd edn. Springer Verlag, Heidelberg and Berlin. 2008; 24.
11. European Commission. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the 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. *Official Journal (OJ)* 2001; Legislation 121: 34-44.
12. European Commission. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. *OJ* 2001; L 311: 67-128.
13. European Economic Community. Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products. *OJ* 1993; L214: 1-21.
14. EC. Regulation 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. *OJ* 2004; L 136: 1-5115.
15. Arzneimittelgesetz (AMG); German Drug Law (GDL) 1961. Gesetz über den Verkehr mit Arzneimitteln. *Bundesgesetzbl I* 1961; 33: 533-546.
16. AMG 1964. Zweites Gesetz zur Änderung des Arzneimittelgesetzes. *Bundesgesetzbl I* 1964; 30: 365-369.
17. AMG 1978. Gesetz zur Neuordnung des Arzneimittelrechts. *Bundesgesetzbl I* 1978; 110: 2445-2481.
18. European Medicines Agency 2009: User Guide for Micro, Small and Medium-sized Enterprises (SMEs) on the administrative and procedural aspects of the provisions, laid down in Regulation (EC) No 726/2004, that are of particular relevance to SMEs (EMEA/430399/2008).
19. Dixit R, Boelsterli A. Healthy animals and animal models of human disease(s) in safety assessment of human pharmaceuticals, including therapeutic antibodies. *Drug Discov Today* 2007; 12: 336-342.
20. Chapman K, Pullen N, Graham M, Ragan I. Preclinical safety testing of monoclonal antibodies: the significance of species relevance. *Nat Rev Drug Discov* 2007; 6: 120-126.
21. Brent RL. Utilization of Animal Studies to Determine the Effects and Human Risks of Environmental Toxicants (Drugs, Chemicals, and Physical Agents). *Pediatrics* 2004; 113: 984-995.
22. Ujházy E, Macha M, Dubovický M et al. Development Toxicology – An Integral Part Of Safety Evaluation Of New Drugs. *Biomed Pap Med Fac Univ Palacky Olomouc Ctech Repub* 2005; 149: 209-212.
23. Prueksaritanont T, Lin JH, Baillie TA. Complicating factors in safety testing of drug metabolites: Kinetic differences between generated and preformed metabolites. *Toxicol Appl Pharmacol* 2006; 217: 143-152.
24. Baldrick, P. Toxicokinetics in preclinical evaluation. *Drug Discov Today* 2003; 8: 127-133.
25. Committee for proprietary medicinal products (CPMP) (within the EMEA). Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). 2002.
26. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH Harmonised Tripartite Guideline: Structure and Content of Clinical Study Reports E3. 1995.
27. CPMP. Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95). 1995
28. CPMP. Note for Guidance on General Considerations for Clinical Trials (CPMP/ICH/291/95). 1998.
29. Härmark L, van Grootheest AC. Pharmacovigilance: methods, recent developments and future perspectives. *Eur J Clin Pharmacol* 2008; 67: 743-752.
30. Colvin L, Slack-Smith L, Stanley FJ, Bower C. Pharmacovigilance in pregnancy using population-based linked datasets. *Pharmacoepidemiol Drug Saf* 2009; 18: 211-225.
31. EC. Eudralex: Volume 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use. 2008.
32. Faden LB, Milne CP. Pharmacovigilance Activities in the United States, European Union and Japan: Harmonic Convergence or Convergent Evolution? *Food & Drug L J* 2008; 63: 683-700.
33. ICH. ICH Harmonised Tripartite Guideline: Pharmacovigilance Planning E2E. 2004.
34. Thalidomide Pharmion Information Brochure. download on 12.08.2009 at http://www.k-faktor.com/contergan/files/thalidomide_monograph.pdf
35. Chambers CD, Polifka JE, Friedman JM. Drug Safety in Pregnant Women and Their Babies: Ignorance Not Bliss. *Clin Pharm Ther* 2008: 181-183.
36. Committee for Meidicinal Products for Human Use (CHMP) (within the EMEA). Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data. EMEA/CHMP/313666/2005.
37. Schaefer C. Off-Label-Use von Medikamenten in der Schwangerschaft. *Frauenarzt* 2007; 48: 21-25.
38. Briggs GG. Better Data Needed from Pregnancy Registries. *Birth Defects Research (Part A)* 2009; 85: 109-111.
39. Pelkonen O. Metabolism and pharmacokinetics in children and the elderly. *Expert Opin Drug Metab Toxicol* 2007; 2: 147-148.
40. Glass LM. Data incompatibility of adverse event reports electronically submitted to the AERS database. *Pharmacoepidemiol Drug Saf* 2008; 17: 209-213.
41. Kola I. The State of Innovation in Drug Development. *Clin Pharmacol Ther* 2008; 83: 227-230.
42. Woosley RL, Cossman J. Drug Development and the FDA's Critical Path Initiative. *Clin Pharmacol Ther* 2007; 81: 129-133.
43. Lesko, LJ. Paving the critical path: how can clinical pharmacology help achieve the vision? *Clin Pharmacol Ther* 2007; 81: 170-177.
44. Forrest MJ, Briscoe RJ, Cumiskey AM et al. Torcetrapib-induced blood pressure elevation is independent of CETP inhibition and is accompanied by increased circulating levels of aldosterone. *Br J Pharmacol* 2008; 154: 1465-1473.
45. Hunter, AJ. The innovative medicines initiative: a pre-competitive initiative to enhance the biomedical science base of Europe to expedite the development of new medicines for patients. *Drug Discov Today* 2008; 13: 371-373.
46. Kamel, L. The Innovative Medicines Initiative (IMI): a new opportunity for scientific collaboration between academia and industry at the European level. *Eur Respir J* 2008; 31: 924-926.
47. Otte A, Rose C, Zaehringer A, Maier-Lenz H. Neue klinische Technologien in der Arzneimittelentwicklung. *Internist* 2008; 49: 232-237.