Patient Registries as Specific Obligations for Marketing Approvals of Orphan Drugs in the European Community

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1. Introduction

The approval of a marketing authorisation for orphan medicinal products (OMP) and for advanced therapies of medicinal products (ATMP) of orphan diseases increasingly includes the establishment of patient registries. This is either already part of the Risk Management Plan already included in the Marketing Authorisation Application (MAA) or an obligation by the Agency, since orphan medicinal products follow the centralised procedure. The reason for this obligation is the authorisation of the product despite incomplete clinical data, which results from on the major challenges of orphan diseases, their low prevalence. The low number of patients in clinical studies cannot reflect the overall possible adverse events and leads to safety concerns by the Agency. For the purpose of epidemiology and post-marketing surveillance, the establishment and implementation of registries and databases [1] actively support the possibility of delivering significant data, which clearly represents the risk versus the benefit of the new medicinal product on the market.

In the European Community the official definition for an orphan disease is defined by its prevalence of 1 in 10.000, whereby prevalence means a given number of patients who suffer from a disease in a population at a defined time point. Orphan diseases are complex and some of these diseases show a prevalence of 1:100.000 or even less. Overall between 5.000 – 8.000 rare diseases have been described, leading to millions of patients being affected, but for each individual disease there are no more than 250.000 patients or even fewer in the European Community [2]. Taking economic aspects into account it can easily be seen that the development of a medicinal product is a challenge for the pharmaceutical industry.

Since 1999 the European Community actively delivered solutions to this challenge. The first step was the implementation of the European legislation regulation 141/2000[3] in 1999 and the commission regulation No 847/2000 in 2000[4]. The European Medicines Agency (EMA) supports the application and approval of OMPs by providing specific incentives to the pharmaceutical industry, like protocol assistance, lower fees in the process of drug application and an exclusive marketing protection accounting for 10 years.
The EC uses two regulatory procedures for marketing approval of OMPs; those are "Conditional Marketing authorisation", laid down in §14(7) of Regulation 726/2004 and amended by Commission Regulation 507/2006[5] and "Approval under exceptional circumstances", laid down in §14(8) of 726/2004. Both kinds of approvals speed up the way to market access and fulfil their tasks for patients who have had no medication up to this time point. The actual application time is in general not shorter than that for normal medicinal drugs, but leads to the possibility of coming to market even though the clinical studies are incomplete. An exception is laid down within Regulation 726/2004, Article 9, defining the

"accelerated assessment procedure" for medicinal products, which are of major interest for public health. In this case the assessment procedure is reduced to 150 days, as was the casefor "Soliris", a medicinal product against the symptoms of the disease Paroxysmal Nocturnal Haemoglobinueria (PNH).

The European Commission Report for Implementation of September 2014 summarised that with the date of January 2014, there were 90 OMPs authorised in the EU and more than 1000 were designated as orphan drugs. Hollak et al[6] describes the "limitations" of previous drug registries that were observed in the past, which were: limited completeness of case ascertainment, limited high quality clinical data and limited verification of data validity as well as limited follow-up measures.

With the implementation of directive 2011/24/EC[7] it became clear that it was necessary to develop a closer interaction between health care systems in all Member States. The overall purpose was the creation of a European Reference Network and a European register platform accompanied by the development of guidance to this platform. Development of standards in data collection and databases for pre- and post-marketing studies are first steps towards a European harmonisation process in establishing a platform for patient registries. One of the first important steps was achieved with the creation and launch of the ENCePP E-Register[8] (EU-PAS Register).

European Reference networks and installation of registers have several important advantages for all stakeholders: they represent a tool for international collaboration in research on rare diseases, they offer unified phenotypic data, they facilitate studies in identifying clinical endpoints or biomarkers, they help in identifying research participants as well as clinical trials. They also support regulatory decisions by enabling data delivery on safety and efficacy, and their usage for general post-marketing surveillance [9]. Looking at the near future patient registries will set a standard in providing good quality data to the European Community, which is also necessary to fulfil "cross border patient´s rights".

The first objective of this master thesis is to provide information and guidance for the installation of patient registries, combined with a reflection of the legal basis according to the latest legislation in the EU.

The second objective is to compare the process and efficacy in installing a patient registry for four medicinal products related to orphan diseases. All OMPs were granted a market authorisation; the years of MA were chosen to lie between 2001 and 2012.

Actually, there is an intensive on-going discussion for joint collaborative actions in the USA and the EU concentrating on approval- and post-marketing phases of orphan drugs. This

collaboration is beyond the scope of this master thesis, which will concentrate on the European requirements.

2. List of Abbreviations

Agency	European Medicines Agency
aHUS	atypical Haemolytic Uremic Syndrome
AR	Assessment Report
ATMP	Advanced Therapy Medicinal Product
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
CM	Chylomicrons
COMP	Committee for Orphan Medicinal Products
CPMP	Committee for Proprietary Medicinal Products
DAA	Drotrecogin Alfa
EC	European Community
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EPIRARE	European Platform for Rare Disease Registries
EUCERD	European Union Committee of Experts on Rare Diseases
EURORDIS	Rare Diseases Europe
FUM	Follow-up Measure
GVP	Guideline on good pharmacovigilance practices
HAHA	Human anti-human antibodies
HCP	Healthcare Professional
HTA	Health Technology Agencies
ICU	Intensive Care Units
ICSR	Individual Case Safety Report
IR	Implementation Regulation
IRDIRC	The international Rare Diseases Research Consortium
IS	Interventional-Study
LPLD	Lipoprotein Lipase Deficiency
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDR	Multi-Drug-Resistance

MGIT	Mycobacteria Growth Indictor Tube
MoCA	Mechanism of Coordinated Access
MoCA-OMP	Mechanism of coordinated Access to Orphan Medicinal Products
MS	Member State
NCA	National Competent Authority
NIS	Non-interventional Study
OMP	Orphan Medicinal Product
ROR	Registry of Registries
PAES	Post Authorisation Efficacy Study
PARENT	Cross border Patient Registries Initiative
PASS	Post Authorisation Safety Study
PNH	Paroxysmal Nocturnal Haemoglobinueria
PRAC	Pharmacovigilance Risk Assessment Committee
PRBC	Peripheral Rec Blood Cell
pp-CM	post-prandial Chylomycronemia
PSUR	Periodic Safety Update Report
PSUSA	Periodic Safety Update Single Assessment
SAG	Scientific Advice Working Group
SCC	Sputum Culture Conversion
SMPC	Summary of Medicinal Product Characteristics
SOB	Specific Obligation
XDR	Extended Resistance
TG	Triglycerides

3. Material and Methods:

The ORPHA.NET [10], a "portal for rare diseases and orphan drugs", is a source of disease registries in Europe. With a status from January 2015, there are a total of 651 registries in Europe, containing in addition 71 global registries. Subtracting the global registries and those, which are not further defined, there is still a total of 576 Registries all over Europe, see table 1. Out of these 651 registries, only 8% are initiated by private companies for the purpose of generating profit with a medicinal product (Fig.1), which reflects a total number of 52 registries. Due to the European support in the development of orphan drugs, the number of registries will soon increase with increasing numbers of approved orphan drugs reaching the market. All Member States have access to the database, with an entry page in each respective language.

Table 1: The Distribution of Registries in Europe

Country	Regional	National	European	Global	Not Defined	Total
TOTAL	77	454	45	71	4	651

Fig.1: Different kinds of Interests in European Registries.

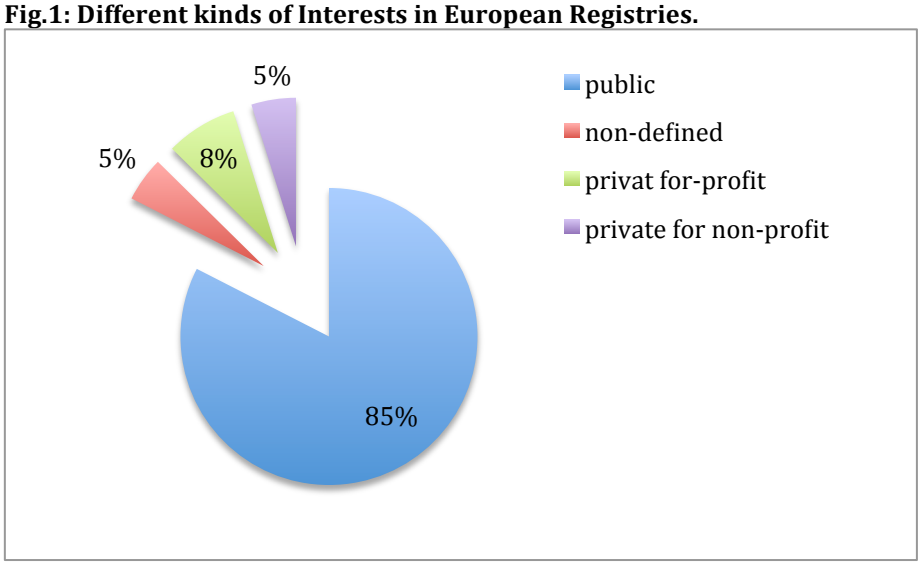


*Figure taken from www.orpha.net

Based on the information from "Orpha.net", four medicinal products (see table 2), designated orphan drugs, were chosen, which all got the obligatory task to initiate a patient registry as a basis for delivering further safety data to support the benefit versus risk of the products.

These 4 orphan drugs were chosen in such a way that their approval dates range from the early beginning of European support, with Regulation 141/2000/EU in 1999, up to 2013, containing also the first European genetically therapeutic product, receiving its approval in 2012.

The aim of this thesis is to monitor the development of patient registries in Europe by working out how patient registries were dealt with in the marketing applications of the drugs analysed. In parallel the period of the last 15 years also reflects the development of the European legislative for the installation of such registries, which is currently closely linked to the new pharmacovigilance legislative of Europe.

Table 2: Four Medicinal Products, with the specific obligation to implement a patient registry as a post-marketing obligation:

Approval number	Product name	INN	Approval	Company	Date of MA
EU/1/12/791/001	Glybera	Alipogenti-parvovec	Exceptional circumstances	UniQure	25.10.2012
EU/1/02/225/002	Xigris	Drotrecogin-alfa	Exceptional circumstances	Eli Lilly NL	22.08.2002 withdrawn on 26.10.2011
EU/1/07/393/001	Soliris	Eculizumab	Exceptional circumstances	Alexion Pharmaceuticals	20.06.2007
EU/1/13/901/001	Sirturo	Bedaquiline	Conditional approval	Janssen-Cilag International NV	19.12.2013

4. Results

4.1. Legal Basis, Overview

4.1.1 Regulations and Directives

Taking the route of the central European approval strategy for orphan medicinal products and fulfilling the new Pharmacovigilance Legislation for post-marketing authorisation, as well as the new dirhective for patient´s rights of cross-border healthcare, the following Community Regulations and Directives are relevant and will be cited within this master thesis. Annex I of this master thesis will cite Regulations and Directives, serving as a quick reference.

- Regulation (EC) No 726/2004, article 14 (7), 14(8), 14(9) [11]
- Regulation (EC) No 726/2004, articles 3(1) and 3(2)
- Regulation (EC) No 726/2004, article 10 and 10a, amended by Regulation 1235/2010.
- Regulation (EC) 726/2004, article 9 (2)
- Regulation (EC) 726/2004, article 23
- Regulation (EC) 726/2004, article 26
- Directive 2001/83/EC, article 8 (3)[12]
- Directive 2001/83/EC, article 21a and 22 and its Annex I, Part II.6 [12]
- Directive 2001/83/EC, article 107m-q
- Directive 2001(837EC, article 108
- Regulation (EC) No 507/2006[5]
- Regulation (EC) 1394/2007 [13]
- Directive 2001/20/EC [14]
- Regulation (EC) 1235/2010 [15] , Article 10 and 10a, amending Regulation 726/2004
- Directive (EC) 2010/84, Article 16, 21a and 22[16], amending Directive 2001/83
- Regulation (EC) No 520/2012**,** Article 36-38 and Article 40 [17]
- Regulation (EC) 847/2000 [4]
- Directive 2011/24/EU, Article 12.4 [5]

4.1.2 Guidelines

Consistent to "Regulations and Directives" the following Guidelines, concerning the topic of Implementing Patient Registries are relevant and will be cited:

- Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to article 14(8) of Regulation No 726/2004, EMEA/357981/2005 [18].
- Guideline on the scientific application and the practical arrangements necessary to implement commission regulation (E) 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of regulation (EC) 726/2004 [19].

- Guideline on good pharmacovigilance practices (GVP). Module V - Risk management systems (Rev1) [20]
- Guideline on good pharmacovigilance practices, Module VI – Management and reporting of adverse reactions to medicinal products [21]
- Guideline on good pharmacovigilance practices (GVP). Module VII – Periodic safety update report (Rev 1) [22]
- Guideline on good pharmacovigilance practices (GVP) – Module VIII – Post authorisation Safety Studies [23]
- Guideline on safety and efficacy follow-up – risk management of advanced therapy medicinial products [24].
- Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies [25]
- EUDRALEX Volume 9A [26]
- ENCePP - Guide on methodological standards in pharmacoepidemiology [27]
- ENCePP - Checklist on Study Protocols (Rev 2, amended)[28]
- Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP)[29]
- Parent: cross border Patient Registries Initiative Guideline [30] (in development, not available yet)

5. Patient Registries and Rare Diseases

5.1 Patient registries - a description

Registries may focus on different objectives, like clinical effectiveness, monitoring of safety concerns, epidemiology, cost-effectiveness or patient outcome. Referring to their objectives registries are differentially classified. Those, which concentrate on a specific patient population being exposed to a new medicinal product, like an OMP, are designated as "**product** or **exposure registries**". The aim of this kind of registry is to prove the benefit/risk-ratio within this special group of patients, as well as the analysis for additional and new adverse events.

Contrary to the exposure registry is the so-called "**disease registr**y", which concentrates on data from patients with the same kind of disease, for example the registry for rheumatoid arthritis. A disease registry gathers all the patients´data, without specific interest in their different therapeutic treatments. These kinds of registries deliver important overviews on patient outcome data.

In case of specific obligations for marketing approvals patient registries are categorized as exposure registries. Their main objective is safety and efficacy, as there are still unresolved safety and efficacy issues because of incomplete clinical data at the time of granting a marketing authorisation. A patient registry is part of the Risk Management Plan and fulfils a proactive risk assessment concerning post-approval marketing time.

For the design of a registry it is important to define the topics, which should be addressed in the registry, including: the size of the registry, the population which will be enrolled, as well as the time of follow-up. Implementing a registry in a real-life setting must consider different aspects, like patient compliance, use of a combination of different medicinal products to be taken, dose effects and probable delayed effects. In case of post-marketing obligations safety aspects are of great importance. It should therefore be ensured, that all aspects of safety information, which is needed, reach all stakeholders: MAH, investigators, patients and authorities. In the case of "Glybera", a gene-therapeutic method, additional safety assessment processes were necessary to reduce the risk of its use. Because of the novelty of *Glybera,* an additional condition concerning the prescription was the restriction that it is only reserved for treatment in a hospital environment by investigators being trained for this kind of new therapy. Observations and documentation of adverse events have to be followed as described in the registry´s standard operating procedures.

In general, the different Stakeholders of Registries are the product manufacturer, competent authorities, authorisation holder, investigators, physicians in general, patients, epidemiologists and health technology agencies (HTA), responsible for all financial aspects of the OMPs.

5.2 ENCePP: European Network of Centers for Pharmacoepidemiology and Pharmacovigilance.

The new Pharmacovigilance Legislation from 2010 claimed transparency to the public for on-going research with medicinal products for human use. One answer to this requirement was the development of an electronic post-authorisation PASS register, designated as EU-PAS Register. The most important tasks in establishing this EU-PAS-Register were fulfilled by the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The "EU-PAS register", hosted by ENCePP, was launched in 2010 [31]. Use of the EU-PAS register is free of charge, voluntary for MAHs conducting voluntary PASS´s, but obligatory for marketing authorisations with an SOB to implement patient registries, like those under exceptional circumstances.

The amended "Declaration of Helsinki from October 2013"[32], now leads to the necessity of registration for every research study involving humans, in a public accessible database.

„Post-authorisation safety studies (PASS) in relation to a medicinal product which are initiated, managed or financed by marketing authorisation holders (MAH) voluntarily or pursuant to an obligation imposed by a competent authority *should also be registered in the ENCePP E-Register of Studies acting temporarily as the EU PAS Register."(www.encepp.eu)*

The objective of the EU-PAS Register and the studies therein is to:

- *„Increase transparency*
- *Reduce publication bias*
- *Promote information exchange*
- *Facilitate collaborations within the scientific community*
- *Facilitate optimal use of expertise in Europe by preventing unnecessary duplication of research " (see ENCePP webpage)*

ENCePP was founded in 2006 and is coordinated by the European Medicines Agency. It represents a voluntary and informal network using data and information delivered from centers specialised in pharmacoepidemiology and pharmacovigilance research.

„The initial priorities of the network were to address the need for (i) transparency, (ii) research standards, (iii) an inventory of data sources and (iv) an inventory of 'study sites'". Results

produced by four working groups include the Code of Conduct [33], the Checklist for Study Protocols [34], the Guide on Methodological Standards [35], the E-Register of Studies and the Research Resources Database [36]."

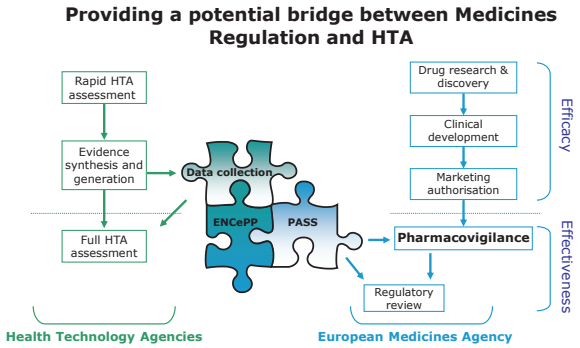
ENCePP comprises of a steering group and the ENCePP plenary group. ENCePP plenary meetings are held twice a year at the EMA, the steering group meets in between these dates. The EFPIA, the European federation of pharmaceutical industry (EFPIA), an ENCePP partner and additional stakeholder with interest in conducting post-marketing studies, is invited as an observer to these meetings. The steering group itself is the organ of final decisions. ENCePP´s most recent Activity Report states that in 2014 the Network comprised of 147 centers, 22 networks and 51 data-sources [37]. By representing 147 professional disease centres, ENCePP is able to provide expertise to authorities and MAHs concerning specific safety concerns in relation to specific diseases.

How to register a PASS in the EU-Pas Register is described in detail in the Guide to EU-PAS-Register[38]. Registering a PASS (i.e. a patient registry) leads to a letter of acknowledgement on registration by the EMA to the MAH. Additionally the EMA will inform all competent authorities of the Member States with" title, name of sponsor, countries, link to registry". Following requests from any competent authority ENCePP provides published and unpublished data. Using this structure (EU-PAS register) ENCePP supports competent authorities by delivering a transparent and reliable basis for decisions on marketing approvals.

Obligations on MA of the centralised procedure leading to the establishment of patient registries or additional post-authorisation activities are laid down in article 10 and 10a of Regulation 726/2004, amended by Regulation 1235/2010, or article 21a and 22 of directive 2001/83, amended by directive 2010/84, respectively. These articles are also the basis of the demanded transparency leading to publishing of protocols and abstract of study-results in the ENCePP E-Register by the Agency.

Figure 2 shows the central role of ENCePP, in creating a new network , the partners of which are the European Medicines Agency, the Health Technology Agencies and ENCePP itself. Data of the Registries and other PASS-Studies are available to all institutions. While the Agency decides on a further positive Benefit to Risk profile and the effectiveness of the medicinal product, as well as on the receipt of the MA, the Health Technology Agencies use the data to analyse for the effectiveness and impact of the medicinal product on the healthcare systems in Europe.

Fig 2: ENCePP and its supporting position for Health Technology Agencies and the EMA



Taken from [39], a poster created by the ENCePP working group on HT-Assessments

5.3 Guidelines and Checklists for the EU-PAS register developed by ENCePP

5.3.1 Code of Conduct and ENCePP Seal

„The aim of the Code of Conduct is to promote and support transparency and scientific independence throughout the research process of pharmacoepidemiology and pharmacovigilance studies." The conduct contains rules and principles referring to pharmacoepidemiology and pharmacovigilance studies, especially concerning post-authorisation studies (including registries). By following these rules it is possible to apply for the ENCePP Seal, which is thought to reflect an increasing trust in the value of study results. Requirements for Seal application are described in detail in the Code of Conduct.

5.3.2 ENCePP - Guide on methodological standards in pharmacoepidemiology

ENCePP developed a guide [35], which gives an overview on methodologies on pharmacoepidemiology and pharmacovigilance, which is annually updated. It is a well-elaborated tool giving electronic access to internationally agreed recommendations, guidelines, published articles and textbooks. It also refers to the US "User-Guide for Registries" regarding topics such as: establishing a registry, maintaining it and evaluating its success [40]. This guide describes also an important topic for orphan drugs, which is the so-called "channelling effect". Typical for new drugs is that they claim advantages over already marketed drugs. This "advantage" may specifically attract patients who show symptoms of pre-existing morbidity and who hope to find help by these new drugs. Prescription of drugs to these patients may entail the risk of the so-called "channelling effect", which incorrectly attributes a disease state to the use of a drug [41]. It is important to be aware of this effect and to define the right patients for the registries. A method to prevent the enrolment of patients

who hope to find help due to those new drugs is to define restrictions. A typical way to define special patient groups is the restriction in form of a prescription for the treatment. Taking Glybera as an example, the restriction was the limitation of treatment to a well-defined population of patients. This well-defined patient-group can be taken as an example to clearly reduce the risk of channelling-effects.

5.3.3 Checklist on Study Protocols (Rev 2, amended)

The ENCePP Checklist on Study Protocols[34] (Annex I) navigates the user by a step-by-step mechanism through the different topics necessary to successfully conduct a non-interventional study. The checklist comprises different topics and each topic is covered by questions referring to the main objectives of these topics. The checklists uses direct questions and direct answers, allowing only for "yes", "no" or "not applicable". If a question is answered with "yes" it is necessary to refer to the specific protocol and point out how this is organized in this specific study. Topics of the checklist are: milestones, research question, main study objective, outcome of interest, confounding by indication, critical uncertainties and challenges in the study design, population, study size, data collection form and power, analysis plan, as well as data management and quality control. This checklist is explicitly recommended for the early phase of planning a non-interventional study (NIS), since all aspects and topics concerned are highlighted and well structured.

5.4 Classification of registries as non-interventional post-authorisation safety and efficacy studies

Post-Authorisation Safety Studies may either belong to Non-Interventional Studies (NIS) or Clinical Trials (CT).

The difference between a non-interventional study and an interventional study is strictly defined by Directive 2001/83/EC, Art 1(15)[42], as well as by Directive 2001/20/EC[43]. Both Directives define a post-authorisation safety study as:

- *„A pharmaco-epidemiological 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."*

For **Non-interventional studies** the following requirements have to be met and need to be fulfilled in a cumulative manner[44]:

1) *The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation*
2) *Assignment of the patient 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

3) *No additional monitoring or diagnostic procedures are applied to the patients and epidemiological methods are used for the analysis of the collected data.*

In case the planned study does fulfil this definition it will not fall within the scope of Directive 2001/20/EC.

According to the differences in interpretations used by different member states, concerning the definition of non-interventional study in relation to the Clinical Trial Directive (2001/20/EC), an ENCePP Task Force Group discussed this issue to solve arising difficulties in conducting those trials where two or more member states are concerned[45]. ENCePP proposes to interpret a non-interventional study in the following way, which is still in line with the definition of Directive 2001/20/EC:

"a study where the medicinal product(s) is (are) prescribed independent to inclusion of the patient in the study and as part of a therapeutic strategy, including diagnostic and monitoring procedure(s), which is not decided in advance by a study protocol but is applied according to the current clinical practice"

EUDRALEX Volume 9A[46] adds an additional definition to distinguish between NIS and IS and opens the possibility on enlarged diagnostics for NIS:

"(…) In this context it is considered important to clarify that interviews, questionnaires and blood samples may be considered as normal clinical practice. Based on these definitions a fundamental distinction can be made between non-interventional (observational) and interventional post-authorisation safety studies. The latter are considered clinical trials falling under the scope of the Directive 2001/20/EC."

EUDRALEX Volume 9A, as well as the guideline for GVP, Module VIII define observational studies as non-interventional studies. In the guideline for GVP, Module VIII and Module V, registries are defined as:

- *„ An organized system that uses **observational study methods** to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.[47,48]. "*

Following the above given definitions for non-interventional studies, Registries are non-interventional studies even though they involve primary data collection. A restriction of primary data collection is that the data is derived from routine clinical care. Methodologies

like interviews, questionnaires and blood samples can be seen as part of normal clinical practice.

GVP, Module VIII, App.1.1 divides "Study Designs" into three different sections: 1) Active Surveillance, 2) Comparative Observational Studies and 3) Clinical Trials. Within this classification "registries" are assigned to the section of **active surveillance**. Using the definition From EUDRALEX Volume 9A and GVP Module VIII, "*an organized system that uses observational study methods*", registries are open to the different methods used by observational studies, which are either cross-sectional studies, or cohort-studies, or case-control studies. M. Thiese recommends in his overview on study designs the case-control-study design as the one design being the most efficient for rare diseases [49]. Participants of the case-control study are identified on the basis of their case status, which means identification on the basis of being diseased or not. Cases are patients receiving the treatment while controls are patients with the disease, but not receiving the treatment. The comparison of the two groups permits a conclusion on the probability of a defined clinical outcome (benefit) or adverse events (risk) in relation to the treatment, or without a causal coherence to the treatment. GVP, Module VIII, recommends simple cohort studies for examining safety concerns of a new OMP. As an advantage of this kind of study, signal amplifications for rare outcomes are indicated.

Non-interventional studies do not in general need ethical approval, but need to be registered at the ethics committees of the European member states. For some member states this may be different and should be evaluated. In case the MAH plans to conduct an NIS (patient registry) in different member states, the local investigator of every country taking part in this study is responsible for registering or applying to the local ethical committee. In case of DNA-analysis being a pre-requisite to ascertain patient suitability for a therapy, it is clearly necessary to apply for an ethics committee approval, since personal sensitive data will be analysed. The International Society for Pharmacoepidemiology recommends a section within the study protocol, which solely concerns the topic of protecting human subjects. This section is clearly meant to be of importance when the study protocol is submitted to an Ethics Committee for official approval. The Guideline for Good Pharmacoepidemiology Practices [50](GPP), section IV is recommended in relation to this topic.

5.5 Requirements for conducting a non-interventional PASS, imposed as an SOB

Post authorisation studies imposed as an obligation by a competent authority are initiated, managed and financed by the marketing authorisation holder (2001/8´3/EC, Art 107m; 726/2004, Art. 28b). Basis for the conduction of registries is Directive 2001/83/EC, Art 107m-q, and Commission Implementing Regulation No 520/2012, Art. 36-38 and Art. 40[51].

The establishment of a Patient Registry is part of the Pharmacovigilance Risk Management Plan of Module I of the Marketing Authorisation Application. An overview of the requirements for conducting a non-interventional PASS for a patient registry (obligation or voluntarily) is given in table 3 and will be described in this section.

Table 3: Non-interventional PASS with SOB: requirements

Management of study	**PASS with MAH involvement**	
	Imposed as an obligation	Conducted voluntarily
1) Request for pre-submission meeting on study protocol	✓	✓
2) Use standard formats of protocol and study report	◆	✓
3) PRAC oversight of study protocol and report	◆	(if in RMP)
4) Registration of study in EU PAS register	◆	✓
5) Study shall not be conducted to promote a medicinal product	◆	◆
6) Payment to HCP restricted to compensation of time and expenses incurred	◆	◆
7) Quality systems	◆	✓
8) ENCePP methodological standards	✓	✓
9) ENCePP checklist for study protocol	✓	✓
10) ENCePP Code of Conduct	✓	✓
11) ENCePP seal	⊙	⊙

Taken from[52] and slightly modified. Legal obligation ◆ Recommended in GVP ✓ Optional ⊙

Table 3 lists requirements, which need to be fulfilled for a submission of a study-protocol when implementing a patient registry, demanded as an obligation by the EMA.

Starting with the date of 15 September 2013 all post-authorisation safety studies need to fulfil the standards for format and content, as given in "Guidance for the format and content of the protocol of NIS post-authorisation safety studies"([22]). PASS protocols submitted before this date were encouraged to use this format or to follow the format given in IR 520/2012 Art 38 and follow the recommendations as given in GVP, Module VIII, section B.5.1.

Concerning older PASS protocols it is much more difficult to compare metadata and data from registries of different member states. The new guidance for format and content brings harmonization to the registries of different member states in relation to metadata used for the PASS. This will enable all stakeholders to search for metadata without losing data, which may have previously had a different coding. Additionally, all PASS will use a defined "Table of content", making it much easier to search for specific study aspects. With the launch of the ENCePP Resource Database, being an inventory of research centres and networks, MAHs, sponsors, investigators, research professionals and authorities have the opportunity to search for information on research experience and specialised centres all over Europe before starting their own PASS. Harmonisation on format and coding may also allow for pooling data

from international and different registries, giving the opportunity to pool data and thereby reach sufficient numbers of patients for statistical analysis.

The protocol for the patient registry will be supervised and assessed by the PRAC. GVP Module VIII, Sections C.4.1 and C.4.2 describe the involvement of the PRAC Committee in protocol approval and study result approval. The process of protocol approval starts with submission of the protocol to the Agency and to the PRAC. In advance to submission it is advisable to request a pre-submission meeting with the Agency, to justify the objectives of the study, the chosen population to be included, as well as expected outcomes, which are dependent on the patient's exposure. After submission of the protocol a PRAC rapporteur will prepare a protocol assessment report and submit this to the PRAC. Within 60 days the PRAC will either approve or reject the study protocol. In cases where the PRAC accepts the proposed study protocol the MAH is responsible for forwarding the protocol to the authorities of concerned member states for the conduct of the study. Concerning EU and national requirements for involvement of ethics committees, these have to be followed.
In cases where the PRAC sends a letter of objection to the MAH, the letter will contain reasons for the objection, an example might be: "*it is considered that the conduct of the study promotes the use of a medicinal product*". Not to conduct studies with the objective to promote usage of the product is also highlighted as an important feature in table 3.

Part of the Approval for the study protocol is the indication of the kind of category to which the study belongs. This is described in the Guideline on GVP, Module V[53]; herein Post-authorisation Safety-Studies (PASS´s) are subdivided into 4 different categories:

Category 1 contains studies imposed as an obligation according to Regulation 726/2004 Art 10 and 10a, and Directive 2001/83 Art 21a and 22a. Category 2 contains studies, which are obligated for marketing authorisations under exceptional circumstances. Category 3 and 4 contain studies, which are conducted voluntarily by the MAH. Category 3 studies are those, which are part of the RMP and evaluate the effectiveness of the Risk Minimisation Activities. Category 4 studies are those, which analyse for safety information with less significance. Referring to these 4 categories, "registries" fall into category 2.

Before conducting a safety study (patient registry), the study has to be registered at the EU-PAS Register, as described in 5.2 of this master thesis:
„Post-authorisation safety studies (PASS) in relation to a medicinal product which are initiated, managed or financed by marketing authorisation holders (MAH) voluntarily or pursuant to an obligation imposed by a competent authority should also be registered in the ENCePP E-Register of Studies acting temporarily as the EU PAS Register."(www.encepp.eu)

By registering a study, the start of data collection and the end of data collection define the frame of the timeline. These two dates delimitate the time schedule for the study conduct and define the date of submission of the final study report to the EMA. Start of data collection is defined as "*the date from which first study subject is first recorded in the study dataset*", while end of data collection is defined as "*the date at which the analytical dataset is completely available"*(IR 520/2012, Article 37).

Concerning "Quality" GVP Module VIII, section B.5.1. defines "Quality of the study protocol":

"a description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification and validation of endpoints, storage of records and archiving of statistical programmes. As appropriate, certification and/or qualifications of any supporting laboratory or research groups should be included."

Since a patient registry, which is implemented as an obligation by the concerned authority, can be audited and inspected by the authority, GVP module VIII, section B.9 also indicates:

„for PASS imposed as an obligation, the marketing authorisation holder shall ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection [IR Art 36]."

"*Registries to Evaluate Patient Outcomes: a User´s guide"*, Section II, describes everyday operational activities and decisions leading to high-quality data in registries. Even though it is the US-version of registries and refers to the US legal requirements, it is worthwhile having a look at it. Also worth looking at is "Guidelines for the conduct of registry based studies using the EBMT Database", which includes an overview of study types, procedures for registry studies, how to administrate these studies, data collection and statistical analysis of retrospective studies [54]

The following terms of references are not obligatory, but recommended in the Guidelines for Good Pharmacovigilance practice: Follow the ENCePP methodological standards, use the ENCePP checklist for study protocols and apply for the ENCePP seal (optional).

Communication and interaction between the MAH, concerned competent authorities of the MS where the active phase of the conducted study takes place and the EMA, are described in table 4.

GVP VIII, section C4 describes the details of the regulatory supervision of non-interventional studies imposed as an obligation to the MAH. During the conduct of the study the competent authority can at any time ask for a study progress report, even though periodically Safety Update Reports will be submitted by the MAH. Sequence and Timing of the PSUR will be

defined with the competent authority and varies between periods of 6 month or once a year. Each PSUR shall describe in a cumulative way the number of patients exposed to the OMP and shall, in detail and also in a cumulative way summarize data, which is of relevance for the benefit to risk ratio of the studied OMP. GVP VII.B.5.8 specifies that all studies conducted (including registries) should be mentioned as an appendix of each PSUR.

Table 4: Requirements during conduct of non-interventional studies

Reporting of study information	**PASS with MAH involvement**	
	Imposed as an obligation	Conducted voluntarily
Protocol and progress reports to be submitted upon request to NCA of MS where study is conducted	◆	◆
Reporting of suspected adverse reactions in studies with primary data collection within 15 days (serious ADRs) or 90 days (non-serious ADRs) *	◆	◆
Final report to be sent to the NCA of the MS where the study is conducted, within 12 months of the end of data collection	◆	◆
Data generated in the study to be monitored with consideration to benefit-risk of product concerned	◆	◆
Any new information which might influence the evaluation of Benefit to Risk balance to be reported to NCAs of MS where the product is authorised	◆	◆
Final report manuscript to be transmitted to NCAs of MS where product is authorised within 15 days after acceptance	✓	✓

Taken from [51] and slightly modified. Legal obligation ◆ Recommended in GVP ✓ Optional ⊙

GVP VIII, section B.6.2 and GVP Module VI, section C1.2 describe the reporting system for occurrence of adverse events during the active conduct of a study. Reports from ICSRs of a non-interventional study will be collected in the EudraVigilance database. Since the Eudravigilance database is devided into two modules, ICSRs will be submitted in the EudraVigilance Post-Authorisation Module (EVPM, as described in GVP Module VI, C.6.2.1. Timelines for transmission are 15 days for serious adverse events and 90 days for non-serious adverse events.

The final study report, an abstract of the final study report and the study protocol must be submitted to the PRAC and the agency at the end of the study (IR 520/2012, Article 38). Annex III of IR 520/2012 describes in detail the format of the documents (see Annex II). Submission is as soon as possible and not later than 12 months after the end of data collection. The protocol and the public abstract will be made public by the Agency on the European Medicines Agency´s web-portal and in the EU E-Register.

6. European Commission Activities for the development of a European Expertise Network and a Platform of European Registries

6.1 European Commission Expert Groups and Projects

With the intention to strengthen research, diagnosis, and therapy, as well as to set a basis for coordinated research on rare diseases in the EU, the European Commission initiated different projects, complying Dir 2011/24/EC, Article 12. The EC 7th Framework Programme, from 2007 to 2013, actively supported topics on rare diseases. A description of some of these expert groups, as well as web-portals on rare diseases, will give a short and comprehensive overview on the European development on this topic and at the same time serves as reference to specialised expert groups. All webpages reflect the development and success in supporting the different topics on rare diseases since the introduction of Reg EC 141/2000.

Table 5: Three examples of European web-based Registries

Name of Registry	Objective	Contact, Web-page
Orphanet	Overview on all registries, national, international, global	www.orpha.net
ENCePP	EU-PAS Register	www.encepp.eu
ROR	Registry of European Registries: share and compare meta-data	http://patientregistries.eu

Three different web-pages offering information on registries, helping MAHs to contact experts on rare diseases, to interact with already existing registries and to register own patient registry.

6.1.1 EUCERD, now Commission Expert Group on Rare Diseases

EUCERD was established in 2009 by the European Commission and was represented by 51 members (representatives from MS, Patients, Industry, Experts and EU-agencies). EUCERD´s mandate ended in July 2013 and has now been replaced by the European Union Committee Expert Group on Rare Diseases [55]. EUCERD´s function was to "*exchange experience, policies and practices in the field of rare diseases, and help the EC and the MS in preparing and implementing activities in the field of rare diseases*" [56]. EUCERD´s first task was the establishment of a European network on Centers of Expertise on Rare Diseases, gathering knowledge on rare diseases on a European level and enabling diagnosis and therapy for European patients. EUCERD itself was a successor organisation of the RDTF, which was established in 2004 by the European Commission.

Until today, rare diseases are not represented in the International Classification of Diseases (ICD10). To change this and start a common designation for the classification of rare diseases,

the EUCERT joint action group worked on a draft for an international rare disease nomenclature [57]. The web page of EUCERD is still active and it is possible to track all activities of EUCERD, of workshops, reports and progress made during these years. EUCERD´s successor organization, the "Commission Expert Group on Rare Diseases" has organised its web page as an interactive and informative platform on topics such as: policy, national plans, reference networks, orphan medicinal products, expert groups and projects.

6.1.2 PARENT JA

- Patient Registries Initiative Joint Action

PARENT was established in 2012 as a three-year running project. The aim of PARENT is [58]:

1) "to rationalise and harmonise the development and governance of patient registries"
2) "to support MS in developing comparable and coherent patient registries
3) "to provide information on the relative efficacy and effectiveness of health technologies"

Parent Joint Action´s main objective is to set up data about existing registries in the European Member States, which was actively achieved and is now ready for usage. The developed "registry of Registries" (ROR) is easily accessible on the Parent´s webpage: http://patientregistries.eu. ROR gives an overview on all registries established in the EU. Still ongoing are activities on the development of a social network for registry holders and users, which should facilitate information sharing and cross-border collaboration.
Beside the development of ROR, additional objectives were to review existing literature in the field of rare diseases and to identify best practice methods for establishment and organisation of registries, as well as to set up guidelines for the establishment of patient registries. A first guideline was developed, which unfortunately is not accessible at the moment on PARENT´s webpage, with the advice that this guideline is under peer review and will soon be available: "Methodological guidelines and recommendations for efficient and rationale governance of patient registries – a draft". The table of contents of this guideline reflects the different topics when implementing a registry. It describes the different kinds of registries, the different topics on creating a registry, the objectives of a registry, handling the data of registries, general requirements for cross-border use of patient registries; it gives an overview on existing EU regulations and examples of legal framework and it also contains the topic of transparency and data privacy, as well as data quality consideration, resource requirements, registry study designs, data analysis and statistical analysis.
Establishing ROR and guidelines by PARENT should be of benefit to all stakeholders, MAH´s as well as competent authorities and researchers in obtaining tools to go with, reduce costs for setting up new registries and help to manage interoperable patient registries.

6.1.3 EPIRARE

- European Platform for Rare Disease Registries

With the demand by the MS authorities or by the Agency on safety- and efficacy-data during the phase of post authorisation, an explosion of patient registries is to be expected. One aim of EPRIRARE is to carry out a feasibility study on regulatory, ethical and technical issues of patient registries, with a specific emphasis on the creation of the European Platform on registries and the data exchange between users. "*The EU Platform for Rare Disease Registries should enable extraction and analysis of rare disease patient data, in the fastest and most efficient way possible, in full respect and protection of patient rights and needs."*
In 2014 EPIRARE published a proposal about a set of indicators for registration of patients in registries [59]. EPIRARE also described the situation of registries in Europe and characterised and classified existing registries [60], [61].

6.1.4 EURORDIS

"EURORDIS is a non-governmental patient-driven alliance of patient organisations representing 676 rare disease patient organisations in 63 countries covering over 4000 diseases."(www.eurordis.org). EURORDIS represents patients in Europe suffering from a rare disease. In addition EURORDIS advocates RD patients at the level of the European Commission as it represents the voice of the patients concerning European policy aspects. EURORDIS offers a platform to its members with information on legal policies in orphan drug development, information on rare diseases, a list of marketing authorisations of orphan drugs, access to orphan drugs in Europe, service to patients and training resources.

EURORDIS is an important partner for the drug developing pharmaceutical industry, since it also offers a platform for communication and information exchange. It is a real advantage for both sides, developer and patient, to have the chance to meet in the early phase of drug development. It is important to know as much as possible about the disease itself and the progression of the disease before conducting a clinical trial.

7. Regulatory lessons from four orphan drugs and their patient registries

In Europe, the official and mandatory way for marketing approval of medicinal products for orphan diseases, as defined in Annex I of REG 726/2004 and ATMP´s, as defined in Article 2 of Regulation (EC) No 1394/2007, is the centralised procedure (REG 726/2004, Art 3(1) and (2)). The four orphan drugs listed in table 1 received a marketing approval either as "under exceptional circumstances" or under "conditional approval". "Exceptional circumstances" hereby describes the fact that the applicant will never be able to provide enough data on the efficacy and safety of the MP, because the disease is rare or ultra-rare and therefore statistically significant data cannot be provided. While a "conditional marketing authorisation" is at the beginning of its approval based on less data, the marketing authorisation can be switched to a standard authorisation with a full dossier when the clinical data is completed. A reason for granting a marketing authorisation under conditional approval can be an unmet medical need. Two of the chosen medicinal products are on the list of medicinal products with additional monitoring as laid down in Art. 23 of REG 726/2004 (Glybera and Sirturo). Glybera is a biological medicinal hproduct, which has not been on the market before, while in case of Sirturo its active Substance has not been on the market before. For these reasons both medicinal products need an additional monitoring for safety reasons. The objective of this sub-part of the master thesis is to describe the development of the chosen products through their marketing authorisation- and post-authorisation process, with a view to the influence of the imposed obligation to implement a patient registry and to describe the influence of this registry on the benefit to risk ratio of these products during their marketing life cycle.

7.1. Xigris – an example of intense discussions and care

Xigris (DAA) received its marketing approval in August 2002 relying on the regulation 2309/93 from 1993, Part A, now changed to 726/2004, specifically defined in Art 3 (1) + (2), plus Annex[63]. The CPMP recommended a marketing approval for Xigris referring to the „*treatment of patients with severe sepsis with multiple organ failure when added to best standard care*", which was later changed to: "*should be considered mainly in situations where therapy can be started within 24 hrs after the onset of organ failure*".
Underlying the life-threatening disease of Severe Sepsis, which is associated with acute organ failure and a procoagulant reaction, is an infection, which causes a release of inflammatory cytokines. Normally human Protein C is converted to Activated Protein C by Thrombin. The transmembrance receptor Thrombomodulin increases the ability of Thrombin to activate Protein C by a factor of 1000. A high percentage of sepsis patients have reduced levels of protein C, which is associated with a high risk of death. This was confirmed in the RESPOND-

phase 2 confirmatory study - using Protein C as a Biomarker[62]. Xigris (DAA) is a recombinant form of the human protein of Activated Protein C and replaces the naturally missing Activated Protein C. Human plasma-derived Activated Protein C plays an important role in the process of coagulation and inflammatory reactions involved in severe sepsis. It shows an antithrombotic effect due to its ability to inactivate the factors Va and Villa and also inhibits the plasminogen-activator inhibitor 1 (PAl-I). This inhibition leaves tissue plasminogen activator in its active form, enabling lysis of fibrin clots. The reduced level of Activated Protein C, seen in severe sepsis patients, may be a consequence of down-regulation of thrombomodulin via inflammatory cytokines.

7.1.1 Xigris: Clinical benefit and Safety concerns – post marketing obligations

The marketing approval for Xigris relied on one pivotal clinical trial (PROWES) only, organized as an international, multi-centre, randomized, double blind, placebo-controlled trial with 1690 patients. The primary objective of this study was to compare the efficacy of DAA against placebo using the primary endpoint of 28-day all cause mortality. The secondary objective was the evaluation of organ function after infusion of DAA. The result of this clinical trial was a reduction in the mortality rate for the DAA treatment-group (24.72%) versus placebo-group (30.83%). The time of the study period was 28 days, which later on was often criticized for being stopped too early.
Adverse Events: DAA showed an overall rate of serious adverse events ranging from 2.1% to 5.4%, being dependent on the number of patients and studies conducted. Clearly significant was the ability of DAA to increase haemorrhage and bleeding. The risk of bleeding was defined in the study protocol and became a clear contraindication for administration of Xigris. Data from PSUR´s and post-authorisation registries showed that "bleeding rates from open post-marketing studies are apparently higher than in controlled trials"

During the pivotal clinical trial 2/3 of patients were treated with heparin and Xigris, while 1/3 of patients received placebo and heparin. The mortality rate was 24.9% versus 28.1%. Since the role of heparin was not clear, the MAH was given the obligation to undergo a clinical trial to clarify if heparin could interfere with the mode of action of Xigris.
Besides the questioned trial for heparin, the MA received further obligations and follow-up measures since the CHMP was of the opinion that "comprehensive information on the safety and efficacy of Xigris cannot be provided by the applicant"[63]. SOBs are listed in table 6. The original list did not contain the establishment of a patient registry.

The MAH was requested to deliver further data on clinical trial post-authorisation, which should serve as a basis for continuously defining the benefit to risk-profile in annual re-assessments.

Table 6: SOB to be fulfilled by the MAH of Xigris

Description	Remarks
Specific Obligation 1: A further clinical study will be conducted to investigate the possible interaction between Xigris and heparin (XPRESS).	Due to 8/07/2002 (Sc. Advice) By end of June 2005 (final study report) Outcome: CHMP stated in 2007 that further to uncertain conclusions of the XPRESS study additional clarification about the benefit /risk ratio is needed
Specific Obligation 2: All bleeding events will be addressed every 6 months by providing a detailed section on bleeding in the PSUR. he first PSUR will be provided within 60 days of 21 November 2002, which is one year after the International Birth Date.	Due to 21/01/03 AR 2005[64]: The CHMP accepted the MAH´s request to discontinue the specific obligation of producing a six monthly bleed report, since no new information was generated during PSUR 1 to 4.
Specific Obligation PROWESS-SHOCK Trial	Requested by CHMP in Feb 2007. MAH: Results available in Q2 2011.

Table 6: originally the SOBs for Xigris did not yet contain a requirement for a patient registry, instead they demanded further clinical trials to analyse safety and efficacy of Xigris.

Up to 2005 the PSUR´s and annual assessments got positive recommendations by the CHMP on the maintenance of the marketing approval for Xigris. At the plenary meeting in April 2005 the CHMP decided to restrict the use of Xigris.

After reviewing the latest available data, the recommendation was that Xigris should only be used for high-risk patients and only in the case of therapy starting within 24 hours of organ failure. At the same time the therapy was restricted to institutions trained for “care of patients with severe sepsis”.

Additional clinical trials to establish the efficacy of Xigris in different kinds of patients were requested by the authorities in Europe and USA:

ADRESS trial: ADRESS was a trial that was requested by the FDA. Included in the trial were adults with a lower risk of death from severe sepsis. Result: no benefit.

PROWESS-SHOCK: the trial was requested by EMA after the annual assessment in 2007, see table 6. Its objective was to generate more data on benefit to risk, randomizing adults with persistent septic shock. Result: no benefit.

In the clinical trials PROWESS, ADRESS and PROWESS-SHOCK no reduction of mortality could be shown compared to placebo. Although the initial PROWESS report seemed to show reduced mortality, the subsequent negative trials lead to a controversy and uncertainties about the benefit of treating patients with Xigris.

Nearly a decade was needed, from 2002 to 2012, to produce significant data and be sure about the fact that Xigris does not show a clear benefit over standard care. During these years the usage of Xigris in intensive care units generated real life data. With time, data from patients receiving Xigris went into different registries for severe sepsis. Originally not being imposed as an obligation by the Agency, these registries were introduced as institutional or local authority-driven registries being focused on the disease "severe sepsis", not on the specific product "Xigris" (see: disease registries, 5.1). Examples are the Italian GIVTI registry[65], the PROGRESS registry[66] or authority-driven registries, like the Belgian Reimbursement Registry on Xigris (using data from the PROGRESS registry on Belgian patients), the UK registry[67], the Polish registry[68] and the French registry[69]. The Italian GIVTI registry concluded that the results "question the way of which the drug is used in everyday clinical practice". The Italian registry showed a high rate of off-label use: "60% of the patients were not treated according to the recommended indication" [70] and the mortality rate (45.4%) was higher than in the initial PROWESS trial.

Overall the results of the clinical trials and the registers were contradictory over a long time. In the PROGRESS registry, 12.492 patients were enrolled of which only 7% of the patients received a therapy containing Xigris. Mortality was comparable between Xigris and non-Xigris patients. In the publication from 2009[66] the author stated that, "after adjustment for imbalances, patients receiving Xigris had a 28% reduction in the odds of death and a relative risk reduction of 17%."

The published report on the PROGRESS registry also discussed results on mortality and disease severity, in comparison to other registries. Registries in general reported higher mortality rates than clinical trials, possibly depending on a higher disease severity of patients in these institutions compared to clinical trials.

The authority driven registries analysed the cost-effectiveness and therapeutic efficacy and stated both as being positive[67,68,69].

A huge amount of literature concerning the use of DAA in clinical trials and observational studies is cited in the yearly CHMP assessment reports, from 2002 up to 2012, reflecting the overall care and concern the committee took, being involved in the benefit to risk assessment.

The PROWESS trial from 2001 showed a reduction of mortality by 8%, while in PROWESS-Shock trial mortality was higher in the Xigris-group (26% versus 24% placebo)[71, 72].

With the results of the PROWESS-SHOCK clinical trial becoming available Eli-Lilly withdrew the product from the market and sent a letter to the EMA with the request for withdrawal in November 2011. The CHMP accepted the withdrawal as being fully justified[73, 74].

During the 10 years of Xigris being on the market there was also a change in the treatment guideline for standard care of sepsis patients, which lead to improvement of care and reduced cases of death. As has been stated in the rapporteur´s assessments report[73], this improvement in standard care may be an important factor, which has reduced the opportunity of Xigris to show benefit over standard care.

General lessons to be drawn from Xigris:

1) Clinical trials use defined criteria for inclusion and exclusion of patients, which do not reflect the everyday patient in the everyday situation in clinical care units.
2) The only pivotal trial leading to marketing approval was stopped too early. It should be general practice to replicate a study before drug approval is possible.
3) Registries were requested by different local authorities, for different reasons. Standardisation of registries was not available at that time point. Results from registries were not comparable.

Xigris is currently an example, which reflects the fact that, with upcoming new substances or new technologies new facts follow that need ways to consider how to react to them. For the last years of development in regulatory affairs these reactions can clearly be described as being the following proactive actions: introduction of RMP´s, risk minimisation activities, the introduction of the European E-Register and its guidelines for standardisation, as well as new upcoming tools for the evaluation of signal detection of adverse events and analysis of therapeutic efficacy.

There is still interest in the analysis of all available data from patients being treated with Xigris. PROTECT is a new tool on "pharmaco-epidemiological research on outcomes of Therapeutics", which is supported by the EU 7th framework and started in 2010[75]. Protect is a multinational consortium of 34 partner, the Agency being one of the partners with the role of coordinating the projects, while Glaxo Smith Kline is the deputy co-ordinator. Xigris is on the working list of PROTECT, unfortunately in a second wave time schedule. There might be the chance of a re-analysis of the Xigris-data. The authors state that such a re-analysis might on the one hand show distinct results and on the other hand may identify early signals that in the past could have accelerated a decision of "Stop or Go on" to earlier time points. In general PROTECT´s aim is to develop tools "*to address limitations of current methods in the field of pharmacoepidemiology and pharmacovigilance*".

7.2 Glybera – Europe´s first approved gene therapy

"Glybera" is the first gene therapy in the EU, which received an MA by the European Medicines Agency in October 2012[76]. Its approval relies on the regulation 726/2004 Art 3(2), containing a new active substance, which has not been on the market before and on REG 1394/2007[13] on medicinal products for new therapies.

The underlying disease requiring a treatment with Glybera is Lipoprotein Lipase Deficiency (LPLD), a severe disease leading to life-threatening pancreatitis attacks even though patients follow a strict nutritional protocol allowing nutritional fat uptake of less than 20% of the normal daily uptake. Underlying the disease itself is a mutation in the lipoprotein lipase gene. Patients with this defect cannot produce enough active LPL, followed by a reduced fat breakdown and an increase in blood fat levels, so-called hypertriglyceridemia. Associated with the disease are several adverse effects like abdominal pain, fatty deposits in skin and retina and the possibility of the development of secondary diseases such as diabetes and cardiovascular disease[77]. LPLD is an ultra-rare disease affecting only one or two people per million.

The active substance of Glybera is Alipogene tiparvovec, an adeno-associated virus carrying the working copy of the LPL-gene. The injection of Glybera into muscle cells leads to the production of the protein and to an actively working enzyme in fat breakdown.

After a long and complex application process, involving the CAT and the CHMP, in the beginning with diverging results on the recommendation for approval, the CHMP at last recommended the granting of a marketing authorisation under exceptional circumstances for Glybera in October 2012. During the approval process Glybera received a negative opinion by the CHMP three times (see Fig. 3). The approval of Glybera raised interest in the community and the regulatory process itself attracted attention. As discussed by Watanabe et al[78], the regulatory tool of "Re-examination", used by the CAT and the CHMP, as well as the requested re-evaluation by the EU commission, were the regulatory tools leading to the granting of a marketing approval for this product. The tool of "Re-examination" is legally defined by article 9 (2) of regulation 726/2004 and article 32(4) of directive 2001/83/EC. After receiving the CHMP´s opinion on the marketing application the applicant had a time window of 15 days to apply for the process of re-examination. Within 60 days the applicant needs to send a detailed report justifying the application of re-examination. The committee itself had also a timeframe of 60 days to analyse and discuss the applicant´s report. The results of the re-examination are part of the final report of the marketing application. The tool of re-evaluation, which can be used by the European Commission after receiving an opinion by the CMPH, is legally defined by article 10 (4) of regulation 72/2004. The described and used tools gave both sides, the applicant and the EMA, the possibility to strengthen the analysis of the data and to shed light

on subgroups of patients and change primary endpoints in clinical trials to patient-related outcome. Finally this regulatory process led to an MA with a restricted indication for administration of Glybera to patients not only with a mutation in the LPL gene, but in addition to patients "with frequent and life-threatening episodes of pancreatitis". This means that in the group of LPL patients Glybera is limited to the subgroup of those patients with the greatest need for treatment.

Fig.3 Timely development of EU regulations and regulatory actions during the development and approval process of Glybera

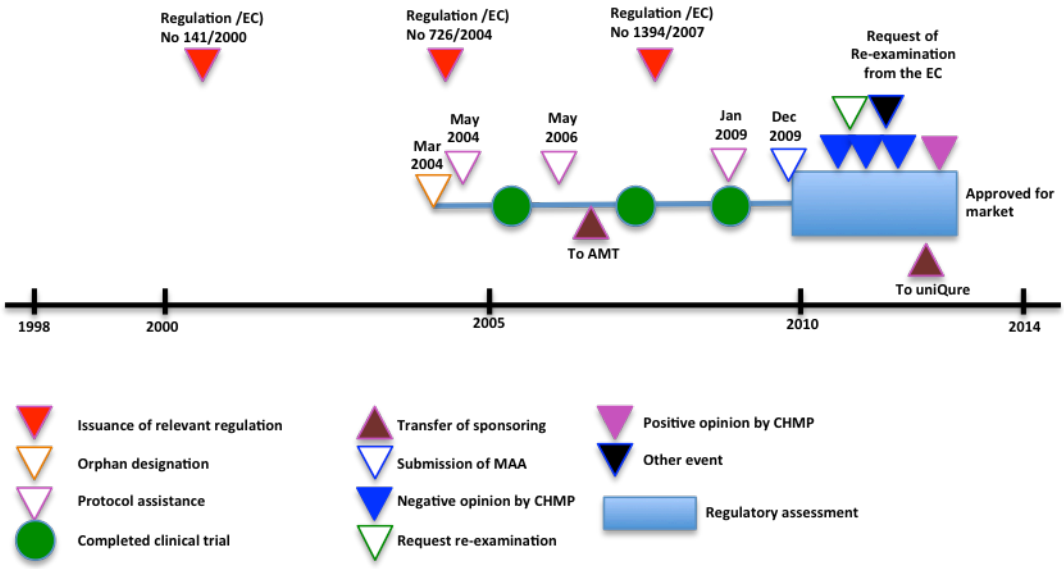


Fig.3. Regulatory activities in the process of marketing application and approval in relation to the time line are shown. The original MAH, AMT, used the instrument for protocol assistance three times before MAA. The MAA was submitted in 2009, the same year the CAT started its work. (Fig. taken from Watanabe et al[78] slightly modified)

7.2.1 Clinical benefit and Safety concerns – post marketing obligations

The basis for clinical benefit was set out in 3 observational studies with 27 patients, aged between 18 and 70 years of age, with a median of 45 years. The observational studies were conducted in the Netherlands and Canada as an open label uncontrolled study. Baseline levels of TG were defined to be >10 mmol/l for each patient included in the study. Protocol assistance for clinical trials was achieved three times (fig. 3).

Endpoints and outcomes of the studies were determined as follows:

„Primary endpoint: reduction in individual median fasting plasma triglyceride levels of: ≤10 mmol/L, concurrent with a low-fat diet, or 40% reduction, concurrent with a low-fat diet. Safety factors: adverse events, vital signs, physical examination, immunogenic response, biologic activity, DNA shedding."

The complexity in deciding on the MA for Glybera is reflected in the assessment reports from the years 2010 to 2012. Any decision about the benefit to risk balance also describes the difficulty in establishing the efficacy of an MP in an ultra-rare disease by using individual patient data. In 2011 the CHMP refused a marketing approval for Glybera. After two "oral explanations" in May and June 2011 the CHMP refused to give a positive recommendation. The Applicant requested a re-examination in July 2011[79]. The MAH concluded that the chosen endpoints (TG <10mmol/L and /or 40% reduction of fasting TG) did not represent clinically correctly chosen markers. The applicant could show that after injection of Glybera the postprandial metabolism of newly formed "large-sized" CM significantly changed. Differences in "large-sized CM" in pre- versus post Glybera-administration were statistically significant. Besides the reduction of large-sized CM the applicant could also show that the event of pancreatitis was reduced at least in some patients, which was supported by the general reduction in hospital admissions and the time patients stayed in intensive care units. The expert group accepted this new clinical finding leading to a change of the endpoint to a surrogate endpoint, being defined as reduction in post-prandial chylomicronemia[80]. The recommendation of the SAG, which was also accepted by the CAT, was to set the endpoint to: 40% reduction of TG and/or reduction of post-prandial chylomicronemia.

In October 2011 the CHMP still did not concur in the CAT´s recommendation but concluded that the safety and efficacy is not sufficiently demonstrated and refused the granting of a marketing authorisation[81].

In January 2012 an EU Standing Committee - Meeting asked the CHMP for a re-examination of the benefit to risk balance in patients with severe or multiple pancreatitis attacks. The CHMP adopted a list of Questions to the MAH concerning the restriction of the indication and requesting an overview of summarized data that would support a restriction of the indication[80].

The data presented by the applicant showed significant reduction in pancreatitis and hospital admission, though patient´s individual data were "fluctuating in the temporal presentation of pancreatitis attacks". The result of the observational studies showed varying lipid reductions; a lowering in fasting lipids by 40% could be achieved in 7 out of 14 subjects after 12 weeks of therapy. The TG lowering was transient and increased again after the time-point of one year after injection of Glybera. Long-term data on lowering chylomicronemia was only available for 3 patients. A reduction in severity or number of pancreatitis could not clearly be shown since the number of patients was too low and the timeframe post-injection was too short[80].

In 2012, after the oral-explanations and the expert group meeting (re-examination), the CAT did recommend:

"Glybera is indicated for adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from at least one pancreatitis episode despite dietary fat restrictions. The

diagnosis of LPLD has to be confirmed by genetic testing. The indication is restricted to patients with detectable levels of LPL protein[80]."

Concerning safety aspects CAT and CHMP were of the opinion: "*in view of the restricted indication of more severe patients, the safety is now considered acceptable….. grounds adopted in October 2011 are considered sufficiently addressed".*

The CHMP claimed further data on pp-CM for supporting the efficacy of Glybera, accompanied by data on pancreatitis and hospitalisation. Given the low number of patients, the efficacy can only be shown by a detailed long-term surveillance (disease registry) for ensuring a safety- and efficacy monitoring; data will be re-assessed every 12 months. Patients should be added to a patient registry and receive a follow-up for 15 years, to analyse the evolution of the disease and to safeguard data against variability, see also table 7.

At that time point the MAH of Glybera was no longer AMT but UniQure, a company that acquired AMT in 2012.

7.2.2 Specific Obligation to complete post-authorisation measures for Glybera

The approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, stated that the MAH should conduct the following obligations, see Table 7.

The Rapporteur´s 150 Days Response Joint Assessment Report[82] from 2010 already showed that the MAH developed an RMP in line with the EU templates. Identified and potential risks, as well as pharmacovigilance activities and risk minimization activities are displayed in this Report. Identified risks were: muscle pain or damage (long-lasting degenerative muscular changes), fever following administration, immune response to capsid gene or transgene (long-lasting inflammatory changes), risks associated with spinal administration of anaesthetic, haematoma, systemic exposure, administration of immunosuppressant drugs (could lead to serious infections), haemorrhage or bleeding, risks associated with stopping anticoagulants, reduced efficacy, risk associated with re-administration, risk of germ line transmission, tumorigenicity, exposure of healthcare professionals and others. Most of the risk factors were dedicated to an observation via the installed registry and connected with specific risk minimization activities. All risk minimization activities were reviewed by the CAT/CHMP. Concerning the risk of re-administration the CAT/CHMP ([82]) does not accept the sole minimization activity of including patients in a registry. An effective solution against re-administration is recommended by the development of education material for Health Care Professionals, it should include the date of birth as well as the initials of the patients[83]. In addition, patients will receive an alert card indicating their disease and treatment in case of general treatment or hospitalization.

Table 7: Specific Obligations for the marketing authorisation granted to Glybera:

Description	Due Date and remarks
The MAH shall set up a long-term surveillance programme/ disease registry to collect information on the epidemiology of the disease and the demographics, safety, and the effectiveness outcomes of patients treated with Glybera. The registry should be performed according to an agreed protocol. The patients enrolled in clinical studies (CT-AMT-Ol0 - 10, CT-AMT 011-01, CT-AMT 011-02) should be followed up in the LPLD registry. All patients treated with Glybera should be enrolled in the registry and systematic data collection carried out to enrich the database: 1)on efficacy data such as biochemical markers as part of normal practice and frequency and severity of pancreatitis and 2) on safety including immunogenicity against Glybera and LPL.	Before launch of the product in each country Protocol should be submitted immediately after the EC decision PSUR/ annual
3) Dietary diary and quality of life data should also be recorded. The diagnosis of LPLD has to be confirmed by genetic testing. 15 years follow-up is recommended for every patient treated.	Re-assessment
Assessment of postprandial chylomicron metabolism in at least 12 patients before and 12 months after treatment with Glybera to be chosen in addition to the patients included in study AMT.011.02; and eight healthy subjects in the second cohort. Assessment of immune response at baseline, 6 months and 12 months in at least 12 newly treated patients. The study should be performed according to an agreed protocol. The study should start by July 2013 and should enrol at least 4 patients per year. Results from the study to be reviewed annually. Re-evaluation of immune responses from all patients enrolled in study CT-AMT-Oll- 01 by using a validated assay method should also be provided. The assay to be used in the study need to be agreed.	December 2017 Protocol should be submitted immediately after the EC decision July 2013 PSUR annual reassessment

*Taken from: CHMP Assessment Report. Glybera, European Medicines Agency. EMA/CHMP/459947/2012, 19 July 2012[80].

The marketing approval states as annex that: „*The Member States shall agree the details of a restricted access programme and a disease registry with the MAH. They shall ensure that Glybera is only supplied if the healthcare professionals involved in the treatment of a patient have received the educational pack and the prescriber confirms that the patient agrees to participate in the registry"[84].*

The original MAH (Amsterdam Molecular Therapeutics) already proposed in its Risk-Management Plan a long-term surveillance of patients for efficacy and safety to be undertaken throughout the EU in the form of a registry, designated LPLD Registry. Data from

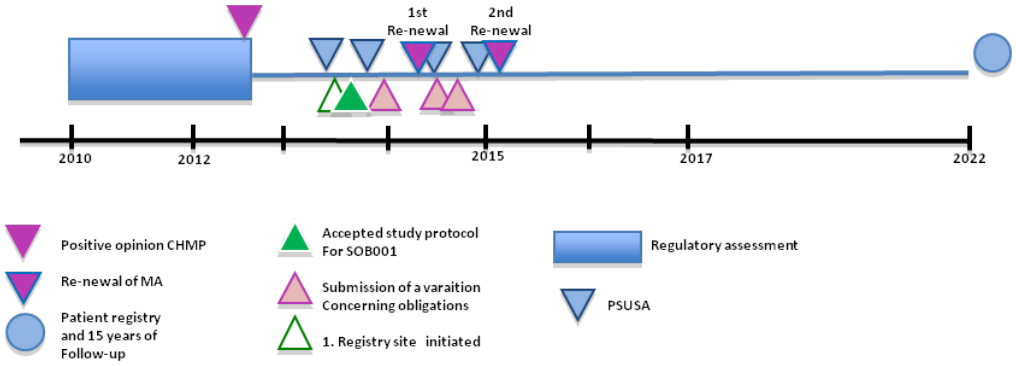
all patients who participated in the clinical development programme as well as those from the post-approval time will be included in this registry.

A study protocol for the post-authorisation safety study (SOB001, patient registry) was presented to the PRAC for review in February 2013. This protocol was rejected since the design did not meet the study objectives. Within 30 days the MAH had to submit a revised PASS protocol to the EMA. In July 2013 the PRAC accepted the protocol for a longitudinal observational registry study involving lipoprotein lipase-deficient (LPLD) patients, who had either been treated with alipogene tiparvovec (see fig. 4) or not. The PRAC did comment that the registry (SOB001) might show the difficulty in getting data from non-treated patients, since in general treated patients are seen more often than non-treated patients.

Periodic Safety Update Reports were submitted regularly and assessed by the PRAC (May 2014[85], October 2014[86], May 2014 and November 2014[87]), all were given a positive recommendation for maintenance of the MA for Glybera.

In February 2014 and February 2015[88], the CHMP conducted the annual re-assessment of the MA for Glybera, with the recommendation from the CAT[89,90] of maintaining the MA under exceptional circumstances[91].

Fig. 4 Post-Authorisation regulatory activities concerning Glybera and its obligations



Glybera received the second re-newal of its MA in February 2015. First registry sites are initiated, but not active yet. Un update of the protocol on post-prandial chymicron efficacy was submitted as variation in September 2014.

7.2.3 Details from the Glybera-registry: follow-up measures.

The report on the second annual re-assessment[88] describes the activities of the MAH to implement the obligations imposed by the EMA. Concerning the LPLD Registry the following activities took place: The protocol for the registry was approved by the PRAC in July 2013[92] (fig. 4) and 3 sites were initiated, two sites in Germany, one in Italy. The first site was initiated in May 2014 in Germany, but none of the patients enrolled is actually treated with

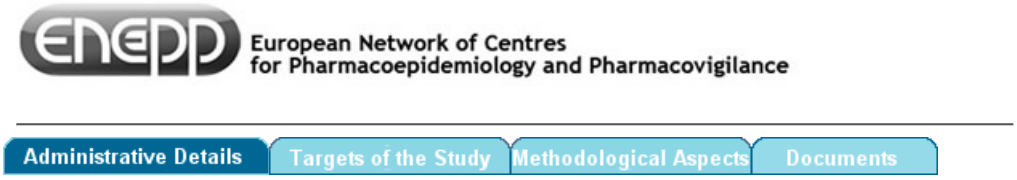
Glybera. In a response to the CHMP the MAH described the initiation of an additional site and further 9 sites planned to participate in the registry study. With the initiation of this new site 7 patients are now enrolled in the registries. Reasons for not seeing patient data in the E-Register is explained by the way that the two sites, that participated in the clinical trials are actively working on the review of the data and on contacting the patients to initiate contracts and consents, as well as on local approvals for implementing the registry. The E-Register itself was launched by the MAH without having the instrument of a case report form at hand. Reason for this approach was the avoidance of any timely delay on this SOB. As a consequence the CAT requested the MAH to follow–up all patients from the clinical trials via the registry before these two registry sites start to enrol new patients. Future PSURs shall provide information on the status of the registry sites, including, if necessary, justifications why patients were not enrolled in the registries.

The ENCePP E-Register holds only administrative information of the LPLD Registry of Glybera. This information relates to targets of the study, methodological aspects and attached documents, such as the study protocol, see fig. 5.
Last up-date of the data in the E-Register was on 17th of June 2015. Up to now no detailed documents on protocols or results of the PASS - registry data are available at the ENCePP E-Register.
A publication by UniQure, from June 2014, on the full-analysis of a six-year follow-up for patients with LPL receiving a single Glybera administration (AMT_011-05 study) gave an overview on the results [93]. The retrospective analysis contained results from 19 patients enrolled in the clinical study. Scott et al, 2015, published similar results[94] for study AMT-011-05 with a follow-up time of 6 years.
"The data shows that these patients have:

. a range of approximately 40-50% of lowered documented pancreatitis events and abdominal pain events consistent with pancreatitis, post-treatment
. no severe pancreatitis up to six years post-treatment
. an approximately 50% lower post-treatment hospitalization rate and number of days spent in the hospital for documented pancreatitis, including only one ICU stay that occurred following treatment[93]. "

Fig. 5: Information on Glybera from the ENCePP E-Register

a)



b)

Status: Ongoing **Last updated on:** 30/03/2015

1. Study identification

Official title:	LPLD Registry, observational longitudinal pharmaco-epidemiologic study in lipoprotein lipase deficient (LPLD) patients, either treated or not treated with alipogene tiparvovec (Glybera®)
Study title acronym	GENIALL LPLD Registry
Study type	Observational study

Brief description of the study

LPLD Registry, observational longitudinal pharmaco-epidemiologic study in lipoprotein lipase deficient (LPLD) patients, either treated or not treated with alipogene tiparvovec (Glybera®), to assess long-term

(*Figure taken from the ENCePP webpage in 2015[95]).

Fig. 5: Data from the ENCePP E-Register for Glybera. a) Overview on the different index cards to various topics of the registry data. b) Pullout of the “administrative details”.

7.3 Soliris - the first approval of a medicinal product for Paroxysmal nocturnal haemoglobinureia

The indication for Soliris is "PNH", paroxysmal nocturnal haemoglobinueria. Soliris is the only medicinal product for this indication and it was the first medicinal product whose marketing authorisation was assessed by an accelerated procedure (Reg. 726/2004, Art 14(9) and designated as an authorisation under exceptional circumstances (Reg 726/2004/ Art 14(8)). PNH is a rare blood disorder, with an estimated prevalence of 13 cases per million, and patients median survival is about 15 years from the time of diagnosis. Life threatening characteristics of the disease are the increased incidence of venous thrombosis, haemolytic anaemia and deficient haematopoiesis[96]. The disease originates in a somatic mutation of the pig-A gene located on the X-chromosome, with a clonal expansion of the affected stem cell, leading to mature erythrocytes being deficient in inhibitory proteins on their membrane, against the human complement system[97]. The active substance of Soliris is the humanized antibody "Eculizumab", directed against the C5 protein of the human complement system. During this pathway the membrane anchored CD59 binds to C5, leading to the activation of the human complement system. The process ends in the formation of the terminal complement complex C5b-C9 leading to lysis of the cell involved in this reaction. Eculizumab binds the C5 protein and prevents the cleavage into the subunits C5a and C5b. By binding to C5 Eculizumab depletes the amount of free C5 protein in human blood and thereby helps stabilising haemoglobin levels.

The development of Eculizumab as a medicinal product against the symptoms of PNH received the orphan drug designation by EMA on 17 October 2003 (fig. 6). Sponsor for the development of Eculizumab was QuadraMed, United Kingdom; in 2006 the sponsorship was transferred to Alexion Pharmaceuticals Inc.. Soliris (eculizumab) is the only medicinal product for this indication. The Applicant asked for protocol assistance twice, in 2004 and 2006. On 29 of June 2006 the CHMP agreed upon an accelerated assessment procedure, with respect to Article 14(9), Reg. 726/2004. On 20 June 2007 Eculizumab was granted a marketing authorisation under "exceptional circumstances", the review process being undertaken within 147 days, see fig. 6. It was the 37th orphan medicinal product receiving a positive CHMP opinion in the EU and the first being accepted for accelerated approval[98]. Soliris did also receive the obligation of implementing a patient registry to collect further safety data, see table 8.

Fig. 6 Timely development of EU regulations and regulatory actions during the development and approval process of Soliris

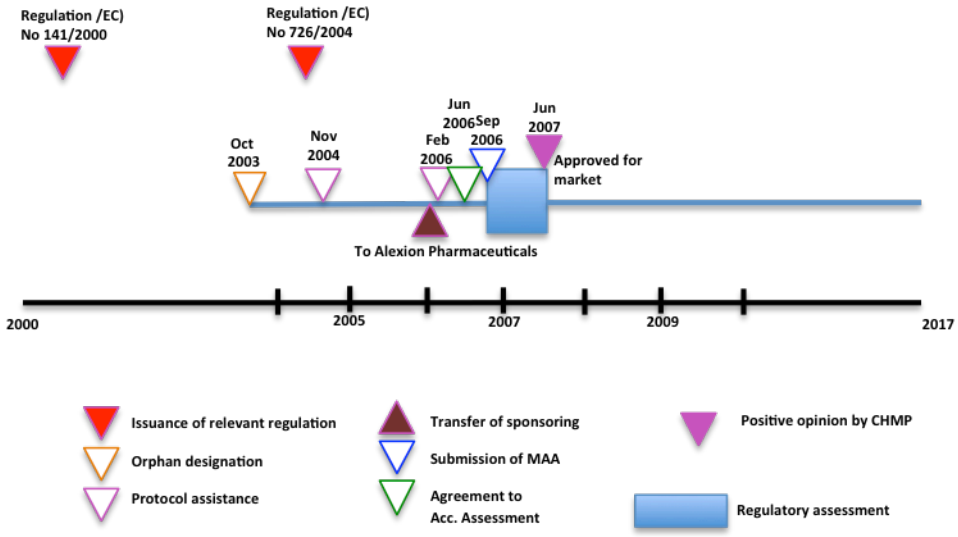


Fig.6. Regulatory activities during the process of marketing application and approval in relation to the time line are shown. The instrument for protocol assistance was used two times before MAA. Accelerated Assessment procedure was accepted in June 2006, the MAA was submitted in September 2006.

Table 8: Obligations to be fulfilled for the marketing-authorisation of Soliris

Obligations	Via	Remarks
Implementation of a PNH Patient registry		X
Restricted access programme	Controlled drug distribution system	Treatment only after written confirmation of vaccination an/or antibiotic prophylaxis
		Vaccination reminders are sent to prescribers
Educational material	Patient safety card	X
	Appropriate educational material for healthcare practitioners, containing:	SMPC
		Guide for prescribing the MP
		Patient´s/carer´s information brochure
		Patient safety card
Patient safety card		Signs and symptoms of infection + sepsis
		Reminder to seek immediate medical care
		a statement that patient is receiving the medicinal product
Patient career guide		Containing and indicating MP specific risks
PSMF		To be in place and functioning before and while product is on the market
RMP		X
RMP updates to be sent to CHMP		X
PSUR cycle		Half-year cycle until otherwise agreed with CHMP

7.3.1 Clinical benefit and Safety concerns – post marketing obligations

The basis for clinical efficacy and safety was set with the treatment of 195 patients who were enrolled in 6 clinical studies; studies were conducted in 13 countries. About 70% were treated for at least 26 weeks and about 20% were treated for nearly 52 weeks [99]. Additional supportive data on safety and efficacy came out of 11 clinical studies, representing additional 716 patients. A further 722 patients were enrolled in studies not related to PNH with a duration from 1 day to nearly 3 years[100].

Efficacy end points of these studies were: stabilised haemoglobin levels, reduction of PRBC transfusion and transfusion avoidance during treatment, LDH (Lactat-Dehydrogenase) – level at the end of study, free haemoglobin, Fatigue-level.

Identified risks of eculizumab in these studies were: general infections, particularly meningococcal infections, haemolyses after eculizumab discontinuation, as well as haematological abnormalities. Even though patients needed to receive a vaccination against Neisseria meningitides, infections did occur. In three cases reported, within the time of application for an MA, one infection occurred in an unvaccinated patient and the other two in vaccinated patients. In the procedure of treatment with Soliris a vaccination is recommended that should be scheduled at least two weeks prior to treatment.

Being aware of the risk of serious infections there are clear contra-indications for the treatment of Soliris, which are: 1) hypersensitivity to eculizumab, murine proteins or to any excipient of Soliris. 2) The following patients should not be treated with Soliris: - with unresolved Neisseria meningitides infection, - patients who are not currently vaccinated and – patients who have hereditary complement deficiencies.

To monitor the safety and efficacy of Soliris a global safety registry had to be implemented. Before launch of the product the applicant had to revise the current safety protocol, as well as to establish an assessment of the immunogenicity of eculizumab in a cohort of patients through the Soliris Registry. The PNH Registry itself was defined as study M07-001 and was started in March 2008. The study is a "*prospective, multi-centre, multi-national, non-interventional study with enrolment of PNH patients treated with Soliris and PNH patients not receiving Soliris therapy. Data is collected at enrolment (after signing the patient´s informed consent) and every six months thereafter.*" The protocol of the registry was approved in February 2008 and amended in December 2010.

The primary objectives of the amended protocol of the registry were/are:

- *The PNH registry collects data to evaluate safety data specific to the use of eculizumab*
- *The registry will collect data to characterize the progression of PNH as well as clinical outcomes, mortality and morbidity in eculizumab and non-eculizumab treated patients*

Secondary objectives are:

- *Raising PNH awareness in the medical community and subject/potential subject population.*

7.3.2 Data-Analysis from the Soliris registry

As is stated on the webpage of Soliris[101], the PNH Registry data is analysed by a collaborative scientific board, chaired by Professor Peter Hillmen, MD, ChB, PhD, Consulting Haematologist, The Leeds Teaching Hospitals, NHS Trust, in England. Up to 2012, the date of the MA-renewal, the MAH submitted 6 PSUR´s. Information from the registry was regularly provided along with the Periodic Safety Up-date Reports (PSUR). These PSUR´s listed the following potential risks identified during therapy with eculizumab: infections, especially for meningitis or encapsulated bacteria, haemolysis after discontinuation, infusion reaction, immunogenicity, hepatobiliary disorder, dermatitis bullous, malignancies, thrombosis after discontinuation, renal disorders, cardiac disorders, convulsions, somnolence, tremor, accelerated Hypertension.
Submitting these PSURs to the CHMP describing the occurrence and identifying the reasons of the ADRs lead to the introduction of additional information into the SMPC, which were:

1) After PSUR 3 in October 2008, section 4.4 of the SMPC was changed to include "Hypersensitivity reactions against infusion".
2) After PSUR 4, the SMPC included Paraesthesia as additional ADR (section 4.8).
3) After PSUR 5, in April 2010, section 4.4 of the SMPC was changed to include that Meningococcal infections occurring in non-vaccinated, but also in vaccinated patients.

Up to 2013 the MAH submitted 9 PSURs. In 2014 the MAH submitted the result of study M07-003 for aHUS–patients as a variation type II, the result of it was requested by the Agency.
The PHN-registry itself was analysed 4 times, a first analysis was performed in September 2011, with a cut-off date of 01 August 2011, 932 patients from 18 countries were included, 69% of the patients being Europeans. The second analysis was performed in February 2012, with a cut-off date of 14 February 2012 and included 1315 patients globally, from which 919 (69%) being Europeans. The third analysis was performed with a cut-off date of 01 February 2013, with a total of 1979 patients. The fourth analysis, from 2014, a requested analysis by the CHMP, was conducted to measure human anti-human antibodies to eculizumab in patients with PNH[102].

The analysis from 2012 tried to ascribe the origin of the ADRs to a specific phase or condition of the patients, for this reason the study population was divided into 5 different groups:

1) "Currently exposed": starting the therapy, up to three weeks after last infusion. This time-window tried to identify risks associated with exposure to treatment.
2) "Recently exposed": three weeks after last infusion to eight weeks after last infusion. This time window tried to identify risks associated with discontinuation of treatment.
3) "Formerly exposed": starting eight weeks after last infusion until the patient experiences an event. This time window tries to identify risks, which might be similar to risks in unexposed patients.
4) "Ever exposed": from the date of first infusion to the occurrence of an event or discontinuation from the registry. This time window tries to identify chronic risks, which might be associated with any treatment exposure.
5) "Unexposed": patients in the PNH registry who never received any Soliris treatment.

The result of the analysis was that 17% of patients reported at least one event, and most of the patients had only one ADR. The patients experiencing more than one event were in the Soliris treatment group. Comparing treated patients versus untreated patients, from the registry, lead to the identification of "infections, malignancies, haemolysis and thrombotic events" as those ADR´s showing a clear difference to the non-treated PNH patients, see table 9.

Table 9: Analysis of ADR´s from 2012 from the patient registry of Soliris

ADR	Main affected subgroup
Infections	Higher incidence of infections in "Currently-exposed patients"
Thrombotic events, plus other major adverse vascular events (MAVE)	Assignment to "Currently-Exposed Patients". After discontinuation, thrombotic events are in general lower, but the highest in "Currently-Exposed Patients".
Malignancies	Occurrence highest in the group of "Ever-Exposed"
Impaired Renal Function	No significant difference between "ever-exposed" and "never-exposed" patients.

The CHMP criticized that the approach shows limitations, especially in: following the protocol that was submitted for the registry, descriptive data among study cohorts, results are not adjusted for confounders, primary objectives were not addressed.

These missing data resulted in a demand of several aspects:

- Providing accurate profiles of the PNH-patients, disease progression, morbidity and mortality, as well as other clinical outcomes.
- Time-to-event analysis, including survival curves, to be generated.
- Rates of discontinuation and reasons for treatment discontinuation to be provided.
- Adjustment of study results for covariant, such as sex, age, PNH history, co-morbidities, medications
- Stratified analysis of sub-populations (PNH sub-types, paediatric population)
- Results on: sepsis, immunogenicity, pregnancy, children-treatment, patients with

renal impairment

- Reminder that the MAH has to submit interim-analysis of the PNH registry with every up-date of the RMP and PSURs.

The analysis from 2013 refers to the statistical analysis plan, version 1.1 from 08 May 2012 and an SAP addendum from 14 February 2013. The same groups were analysed as described above: current exposure, recent exposure, former exposure and ever exposed. The analysis addressed the former demanded aspects resulting from the 2012 analysis by the CHMP[103]. The main ADR´s are shown in Table 10. For "Infections" the cumulative incidence of infections is higher in treated patients than in never treated patients (9.5 % versus 2.7%). After controlling for a Hazard Ratio, the treated patient group still has a risk, which is twice as high as for the untreated group. Mortality was higher in patients who were never treated with eculizumab than in treated patients (3.67 vs 0.97 per 100 patient years). After 1 year of treatment the cumulative incidence for death was 4.9 % for untreated patients and 1.0% for treated patients. After 4 years of treatment the cumulative incidence of death changed to 10.2% in untreated patients versus 5.1% in treated patients.

Table 10: Analysis of ADR´s from 2013 from the patient registry of Soliris

ADR	Main affected subgroup
Infections	Currently exposed patients/non-treated patients. Neisseria Infections: 8/0 (9.5 % versus 2.7%).
Thrombotic events, plus other major adverse vascular events (MAVE)	Untreated patients 1.25 vs 0.79 per 100 patient years
Malignancies	Ever-treated patients/ Never-treated patients 1.37 vs 0.87 per 100 patient years
Haemolysis	Treated-patients/never-treated patients 4.41 vs 4.06 per 100 patient years
Infusion reactions	In general 5.2%, none in patiencts <18 years of age.
Immunogenicity reactions	Starting the treatment: occurring in 3 patients
Pregnancy	Treated/un-treated patients: 2.74 vs 1.76 per 100 patient years).
Deaths	66 deaths reported during follow-up time within the registry. 42 in un-treated patients, 15 during current treatment exposure, 5 during recent exposure, 4 during former exposure, (3.67 versus 0.97 per 100 patient years).

The PRAC concluded from the PNH registry results of 2013 that malignancies are a major risk of the treatment. The next PSUR should therefore include and present a "line-listing-split", splitting treated vs non-treated patients, solid vs haematological malignancy as well as type of cancer. For the aHUS registry a safety report is requested for the next interim analysis.

Based on the safety data the MAH was told to change section 4.8 of the SMPC to include Aspergillus infection and up-date the RMP with the identified new risk for Aspergillus infection in the context of transplantation.

The summary of safety concern listed the important identified risks, important potential risks, as well as the important missing information.

The conclusion of the PRAC and CHMP was that Soliris still has a positive benefit to risk balance and that no new important safety concerns arose.

The fourth analysis of data, which was requested by the CHMP and which was delivered by the MAH as a variation type II, was a non-therapeutic research study, which was designed for the collection of data on human anti-human antibodies (HAHA), which might be associated with long-term use in patients being treated with Soliris. For this analysis patients were enrolled, who had participated in the clinical studies E001-05, as well as in the studies TRIUMPH, SHEPERD and X03-001.

Study objectives were:

- Identify proportion of patients who developed neutralizing antibodies against Soliris
- Identify proportion of patients who developed non-neutralizing antibodies and identify patients who developed neutralizing antibodies with evidence of increased haemolysis.

Altogether 187 patients participated in this study for a time of 120 weeks. Out of these 187 patients, 119 were eligible and enrolled in this non-therapeutic study. Several patients discontinued the treatment, leaving 74 eligible patients, who were treated with Soliris between 6.5 and 10.8 years. No HAHA were identified in patients treated with Soliris in a long time manner. Since this was on open question during the previous PSURs, the result of this study did not lead to a change in the SMPC. The CHMP concluded that benefit to risk ratio of Soliris remains unchanged.

On 26 February 2015, the CHMP accepted a change to the indication. The indication of Soliris is no longer restricted to patients with a history of transfusions, but open to PNH patients with symptoms pointing to high disease activity, regardless of transfusion history[104].

7.3.3 Signal and Risk Evaluation for Soliris:

An important fact of collected data, produced during the post-marketing period, is the description of potential and identified risks, as well as the rejection of signals due to scientific evaluation of the medicinal products. The PRAC assessment report from 2013 led to the closure of categorized risks as well as to the closure of rejected signals.

- Closure of identified risks: haemolysis after discontinuation, infusion reactions, immunogenicity, serious infections and malignancies, just to report the important risks.
- Closure of rejected signals for: hepatic disorders, hypersensitivity, somnolence, dyspnoea, dermatitis bullous, and others, cited in the report.

The long-term follow up of this orphan drug clearly showed which kind of risks are concurrent risks, being realistic and will receive an on-going observation via the pharmacovigilance system and the PNH registry of the MAH. It also shows which kind of risks are signals that are not related to a treatment with Soliris.

Up to now Soliris is not registered in the ENCePP E-Register. Neither is any data from the registry nor any published PASS by EMA found in the ENCePP E-Register. The SMPC of Soliris does contain information on the results of the PNH registry (M07-001), giving patients direct information on patient-outcome concerning LDH-levels and FACIT-Fatigue score. The company Alexion Pharmaceuticals Inc. actively maintains a webpage directing to the Soliris PNH Registry: http://www.soliris.net/hcp/pnh-registry. This website describes the kind of study conducted, the countries in which the study is conducted, the number of patients enrolled in the study and the benefit of taking part in the registry as a patient. This registry fulfils the obligation of implementing a patient registry, with all information patients and healthcare professionals need, but it lacks the activity to register at the European E-Register.

After a marketing period of 5 years and the application for renewal of the marketing authorisation in 2012, the CHMP "considered by consensus that": the benefit to risk profile for Soliris is still favourable and that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated[105]. They granted a renewal on 15 March 2012. Along with the renewal of Soliris for PNH, the applicant applied for an MA for Soliris with the indication of "atypical Haemolytic Uremic Syndrome" (aHUS). Obligations for both indications are the continuation of patient registries. Further obligations were the production of patient´s guides and patient safety cards. Both should include the description of specific risks alongside Soliris, as described above. The patients carry patient safety cards at all times, so that any healthcare professional coming into contact with this patient knows that the patient is being treated with eculizumab.

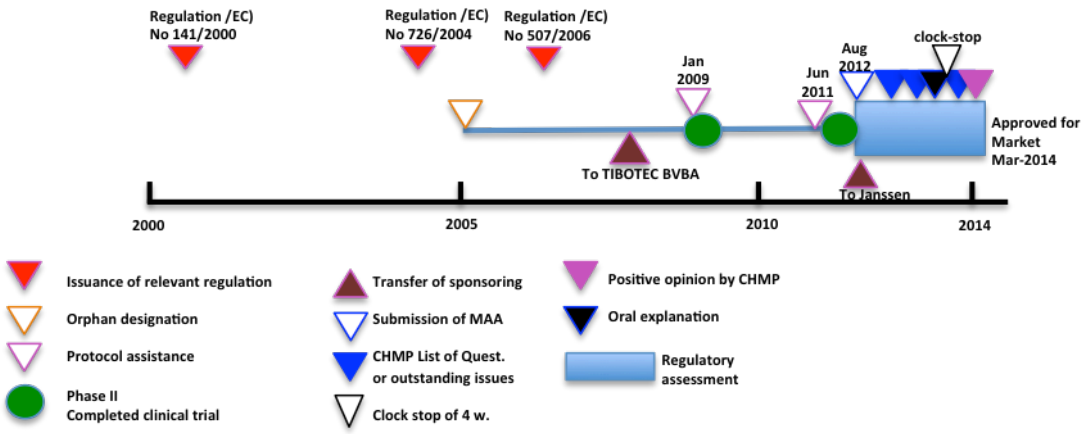
7.4 Sirturo – after decades a new drug against multidrug-resistant strains in Tuberculosis

In March 2014 a marketing authorisation with 10 years market exclusivity was granted to Sirturo. Since clinical data was limited by the time of MAA, but superiority could be shown to some extend, the MA was granted under conditional approval[106].

The approval relies on regulation 726/2004, Art 3(1), No. 4 of Annex of 726/2004, containing a new active substance, which has not been on the market before and being an orphan medicinal product, according to regulation 141/2000, as well as on 726/2004, Art 14(7) and on regulation 507/2006 for a conditional marketing authorisation. Contrary to marketing authorisations under exceptional circumstances the conditional marketing authorisations are not intended to be kept under this restriction, but to develop into a full marketing authorisation with time.

The indication of Sirturo is Multi-Drug-resistant (MDR)-Tubercolosis (TB), caused by an infection with mycobacterium tuberculosis. Sirturo is given as part of a combination therapy for adult patients, being older than 18 years. In August 2005, the European Commission granted orphan designation to Sirturo. Sirturo (Bedaquiline) is the only orphan medicinal product against MDR-TB. At the time of orphan drug designation Sirturo was a product of Tibotec Pharmaceuticals, Ireland. In September 2012 this orphan drug designation was transferred to Janssen Cilag in a two-step modus, see fig. 7.

Fig. 7: Timely development of EU regulations and regulatory actions during the development and approval process of Sirturo



Being a medicinal product, which meets an unmet medical need of patients, Sirturo did benefit from Reg 507/2006 and received a marketing authorisation under condtional approval.

TB can be a fatal disease with nearly 9 million people infected worldwide in 2011. Subgroups of patients develop resistance to anti-TB agents. “Multi-Drug Resistance” (MDR) is defined by in-vitro resistance against two first-line anti-tuberculotica, like rifampicin and isoniazid.

Besides MDR bacteria develop additional resistances agains anti-tuberculotica. This "Extended Resistance" (XDR) is defined as in-vitro resistance against two first-line antibiotics and at least one second-line antibiotic. About 5% of TB patients belong to the MDR-group. In 2012 the numbers of TB cases for the European Union were estimated to be 1.6 cases per 100.000 persons, while outside of the EU numbers are estimated to be 16.8 cases per 100.000 persons[107]. In Europe, the prevalence of MDR is about 15% for new diagnosed TB patients. This number increases up to 47% for patients who have been treated against TB[108]. The estimated numbers of TB-patients differs, depending on their relative location in Europe, see fig. 8. Data based on numbers of the Committee for Orphan Medicinal Products (COMP) state that MDR-TB affects about 2 in 10.000 people in Europe[109]. A surveillance report from 2014 described the treatment success for MDR TB in Europe to be 32.2% and 19.1% for XDR[110]. Worldwide MDR-TB patients reached a number of 630.000 cases[111].

The active substance of Sirturo is Bedaquiline, an antibiotic of a new class and specific for Mycobacteria. The effect against Mycobacteria relies on an inhibition of the bacterial ATP-Synthase, leading to death of those bacteria who are susceptible to the drug.

Fig. 8: Incidence of TB in different countries from TBnet in Europe*

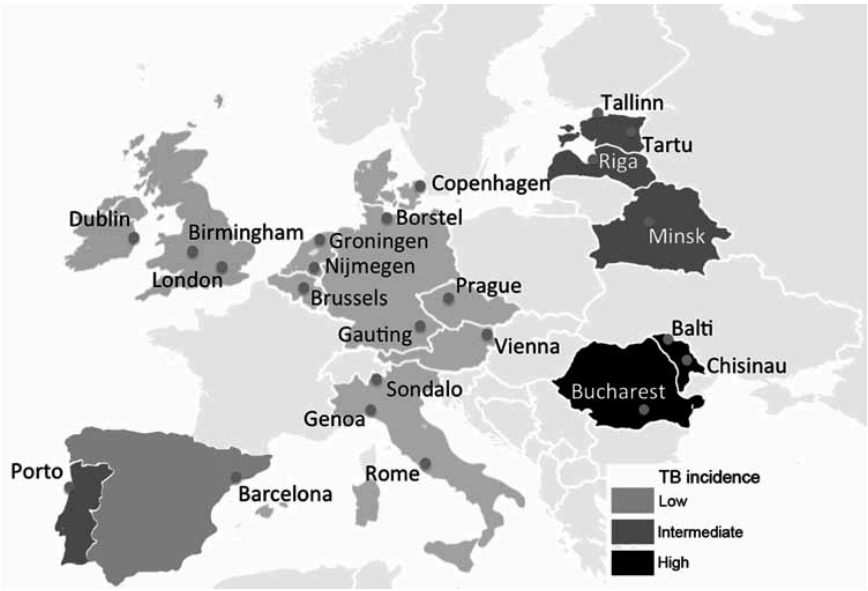


*Figure 8: taken from www.cdc.gov/eid • Vol. 21, No. 3, March 2015. Low TB incidence, <20 cases/100,000 people; intermediate TB incidence, 20–100 cases/100,000 people; high TB incidence, >100 cases/100,000 people.

7.4.1 Clinical benefit and Safety concerns – post marketing obligations

Clinical trials were designed as placebo-controlled and non-controlled trials. The basis for clinical efficacy was set in two completed clinical phase II studies (C202 and C208) and one on-going phase IIb study (C209) by the time of submission of the MAA. C208 was divided in two separate parts, a treatment time of 8 weeks and a treatment time of 24 weeks, including overall 207 patients. End of the trial was at week 104. Sirturo was only given during the first 6 months of diagnosed TB, which are described as "intensive treatment phase". The background regimen was a treatment with a combination of 5 Antibiotics for 18-24 months, respectively. Treatment was adjusted to the WHO recommendations for treatment of MDR-TB[112].

Objectives of the clinical phase II studies were:

a) C208, stage 1: "*evaluation of the PK, antibacterial activity, safety and tolerability of bedaquiline compared to placebo[113].*"

b) C208, stage 2: "*demonstrate superiority in the antibacterial activity of bedaquiline compared to placebo"[113].*

The chosen primary efficacy endpoint was „time to sputum culture conversion (SCC)", which describes the time window needed until the culture does not show any growth of mycobacteria. The secondary efficacy endpoint was "Culture Conversion Rates". This rate shows the amount of patients who responded to the treatment versus the amount not responding to the treatment. Additional secondary endpoints were: time to positive signal in MGIT, changes in CFU counts, changes in chest X-Ray, changes in weight. Patients were defined to be cured when the SCC was negative five times for the final 12 months of treatment. Result for clinical efficacy was the demonstration of antimicrobial activity, with superiority for time of culture conversion and conversion rates compared to placebo (background treatment). Time to culture conversion after 24 weeks was 70 days in comparison to 126 days for the placebo group[112].

Safety evaluation for bedaquiline was based on 11 phase I trials and 3 phase II trials, with a number of patients of 645 persons[113]. Serious adverse events concerning toxicity of bedaquiline were uncommon in comparison to placebo. A first impression shed negative light on the bedaquiline group concerning "Death Rate" of patients. In comparison to placebo the rate was higher in the bedquiline groupt (2 versus 10). The company did explain this effect with the fact that these deaths did occur during the follow-up phase at very much later time points and were non-TB related. None of the patients who died did show a QT-effect during regularly monitoring.

In laboratory measures only liver enzymes were found to show an effect on bedaquiline. This fact has to be clarified for future studies, leading to monitoring of liver toxicity and was discussed concerning labelling.

QTc-intervals did significantly increase in the bedaquiline group of study C208 and C209. Although a direct influence could be shown on QTc-intervals due to bedaquiline treatment, this increase was defined as being moderate (15 ms versus 10ms defined for drug development).

The RMP of the company does include a multi-country MDR-TB registry, which was confirmed by the PRAC and CHMP in consensus. The registry will *"evaluate the effectiveness, safety and drug resistance of bedaquiline when added to a Background Regimen*[114]*".* The safety concerns referred to in the registry are: "increase in QT interval, serious liver effects, inflammation of the pancreas, muscular disease, damage to heart muscle, development of drug resistance, off-label use, medication error, long term-effects, use in elderly patients, use in patients with MDR-TB and HIV, effects on fundic glands, drug-drug interactions. Reports from the registry will be up-dated every 6-month, the final registry study report is expected to be finished at Q2 of 2020. For a second, independent US-registry final results are expected for 2019. Objectives of this registry are the "*description of the indication and utilisation of bedaquiline, patient outcomes, drug-susceptibility and adverse events*[114]".

Since the RMP of Sirturo does already contain two registries addressing the specific safety concerns, the registry itself is not addressed as an obligation, but as a *"condition or restriction with regard to the safe and effective use of the medicinal product*"[113].

7.4.2 Data-Analysis from the Sirturo registry - follow-up measures.

First information from the registry for Sirturo is brought up in the PRAC PSUR assessment report from 2015, covering the period from December 2012 to September 2014. So far the MAH "Janssen-Cilag Inernational N.V." did only implement the Exposure Registry in USA, designated "TMC207TBBC4001". The European Multi-Country MDR-TB registry planned seems not to be set in place, no registry data on this medicinal product can be found in the ENCEPP E-Register up to now, nor in any EMA report. The Periodic Safety Update Report (PSUR) mentions that only 1 patient was enrolled in the American registry[115]. Data from this one person does not have an impact on the benefit-to-risk ratio of Sirturo.
At the moment additional efficacy and safety information on bedaquiline do come from on-going post-authorisation trials, as there are:

- TMC207TBC3001: an early access trial of bedaquiline in the treatment of X-MDR.

- TMC207TBC3002: an expanded access programme of bedaquiline for longer treatment time
- 1 completed TB Alliance sponsored clinical trial (NC-003)
- confirmatory Phase III study (STREAM), data will be presented and updated with annual renewal process

The completed trial NC003 did show no new safety concerns. 60 people were treated and the treatment was tolerated well and was safe.

The clinical trials C208 and C209 were finished and the final study results were submitted as a grouped variation in September 2014, see fig. 9. Additional new information did not arose, neither in relation to efficacy, nor in relation to safety[116]. A second variation concerned the up-date of the SMPC in relation to the final study of carcinogenicity studies in rats. Results were in accordance with earlier results. The third variation did relate to the packaging site.

Fig. 9: overview on regulatory post-authorisation activities for Sirturo[117]

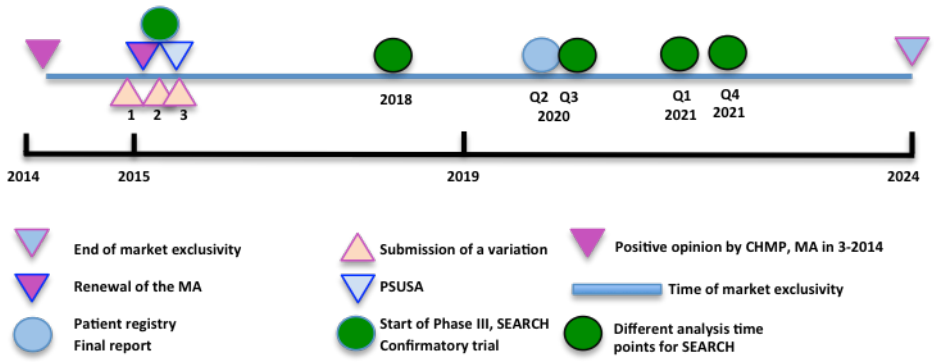


Figure 9: Following the marketing authorisation under conditional approval, three variations were submitted up to now, and a first PSUSA. The first renewal of Sirturo was granted in January 2015. Final analysis of the patient registry is expected for Q2 of 2020, final report of the confirmatory phase III trial is expected for Q4 in 2021.

In addition to other requests, the CHMP requested the MAH during the first renewal of Sirturo , to deliver data from the US registry and to show the establishment of the multy-country prospective MDR-TB patient registry in Europe within the next PSUR[116].

8. Summary and Conclusion

This master thesis gives an overview on the legal framework for the establishment of patient registries and describes the influence of data from patient registries in the post-authorisation phase of orphan drugs and ATMPs, reflecting patient data from everyday life.

Patient registries can clearly be differentiated from clinical trials, as described in section 5.4. Registries imposed as obligations are by definition "product or exposure registries" and are conducted as non-interventional post-authorisation studies.
With the development of ENCePP a network of competence in Pharmacoepidemiology and Pharmacovigilance was created, which laid down the methodology for good quality criteria of registry-data, an electronic platform, the European E-register, and a basis for communicative interactions between experts and all stakeholders in the development of orphan drugs and ATMPs. Section 5.5 describes the requirements for managing a patient registry and the requirements during the conduct of patient registries.

Four medicinal products were depicted as examples, whereby every single one of the four has its own specificity.
Working on the different documents of PRAC-, CAT-, and CHMP-assessment reports, as well as the submitted documents of Module 2.5 and 2.7 of the original application dossier of the four MPs, clearly shows that the MAHs were skilful in embedding patient registries in their Risk Management Plans and develop the necessary protocols for the establishment of the registries.

8.1 Publication of registry – data:

The MAH of Glybera is the only one of the four MAHs who already submitted documents to the registry at the European E-Register, though the company is not actively operating this registry, nor treating any new patient. Contradictory to Glybera the MAHs of Soliris and Sirturo actively treat patients and operate their patient registries, but have not submitted their patient registries at the European E-Register (table 11). Legally publication of the documents through the E-Register will be carried out by the Agency after the final study report has been submitted, as laid down in article 38 of IR 520/2012.
Xigris cannot be taken into this comparison, since it was already withdrawn from the market in 2011 and information about Xigris patient registries cannot be found any more, neither on the company's web page nor in the E-Register.
For the other medicinal products information on the patient registry can either be taken from the E-Register or from the company´s web-pages.

The contradictory picture for the three orphan drugs, which are on the market, may be characteristic for an interim period of new legal frameworks. Although the European E-Register was launched in 2010 and already contains hundreds of studies it seems to be an instrument that is not easily adopted by the pharmaceutical industry.

For Glybera, the European E-Register displays detailed information on the patient registry. It describes the kind of registry, the coordinating study entity, gives information about the primary lead investigator, the number of centres and countries which participate, the amount of patients planned to be enrolled in the registry and the study timelines. It also gives a direct contact detail for scientific and public enquiries and more.
In contrast to this informative description on administrative information, Soliris has its own web page, located in the US (table 11). This webpage directly invites physicians to enrol their patients in the patient registry. Besides detailed information on the disease itself, the webpage gives the possibility to download the Soliris brochure, in which all countries are described that are actively involved in the installation of patient registries for the treatment with Solirus, including European countries. Though this webpage is very informative it is not possible to find any information about European contact details.

Table 11: Data administration on patient registries at the European E-Register by MAHs

Product	Company	European E-Register	Company´s web page on patient registry
Xigris	Eli Lilly NL	-	-
Glybera	uniQure	+	-/+
Soliris	Alexion Pharm	-	http://www.soliris.net/indications/index.php +
Sirturo	Janssen Cilag Ph.	-	https://www.sirturo.com/ (-)

The shorthand symbols stand for the following information: "-"= no information to find on patient registry. "-/+"= only informal information to find about patient registry. "+"= Detailed document information to find about patient registry.

Sirturo is also described in detail on its own webpage (table 11). But no information can be found about patient registries at all. In case a physician uses this webpage for first information and available up date in the life-cycle of the medicinal product "Soliris", he will not receive any information about the possibility to enrol his patient in the Soliris-registry.

8.2 Impact of registry-data on the marketing authorisation:

Though not being directly transparent to the public, data from the patient registries have an impact on the use during the life cycle of the products. This impact is set by the regular

analysis of data from the patient registries, either submitted directly with the PSURs or requested by the Agency. Direct data impact from the registry will find its way into the SMPC of the medicinal product. Section 4.4 of the SMPC of Soliris now includes hypersensitivity reactions against infusion as special warning and precaution, as well as the fact, that meningococcal infections occur in non-vaccinated but also vaccinated patients. Section 4.8 of the SMPC now includes paraesthesia as an additional ADR of Soliris treatment.
Unfortunately the registry for Glybera is not active, therefore no influence of the registry to the SMPC can be observed. The same is true for Sirturo, which in the moment includes only one patient.

Besides direct implication of changes to the SMPC the regular submission of data from the patient registry enables PRAC to concentrate on specific events and to request for further data on specific observations. In the Soliris registry malignancies were considered to be a specific risk. Further ongoing analysis of this topic will try to specifiy the kind of tumours concurrent to this kind of therapy.
A general limitation of patient registries for orphan diseases is the limitation of patient numbers and number of events. But the advantage of registries is to deliver those kinds of data, which come from "normal day patients", who may be more severely diseased than patients enrolled in clinical post – authorisation trials.

8.3 Harmonisation processes for the production of high quality data

With expansion into global markets it is of crucial importance to get sound baseline data from patients with their different epidemiological background, especially for orphan drugs. Patient registries have the ability to produce this kind of data[118]. In the today´s global market it is of importance that manufacturer, as well as authorities, concentrate on a proactive approach to the phase of pharmacovigilance, the basis of which is laid down by the introduction of RMPs and risk minimization activities through Regulation 1235/2010 and Implementation Regulation 520/2012, as well as the introduction of patient registries in case of orphan drugs and ATMPs. Enforcement of these kinds of proactive approaches will improve the focus on safety aspects already during clinical development. As a result post-authorisation data will more easily and reliable be added to clinical trial data concerning efficacy and safety.

The withdrawal of Xigris in 2011 is a famous example of a regulatory affair case, which opened the discussion on how to guarantee safety and efficacy of medicinal products for orphan diseases. Poole et al[71] did criticise the EMA as well as the FDA for failure in their duties, leaving EMA with "the merit of having requested the confirmatory trial, but years too late". The authors charge both institutions and request the obligation that both authorities

have the task „towards the public and the research community, to ensure that research is not compromised by conflicts of interests“. They do also state that “the standards for marketing approval did dramatically lower in the pretext of unmet medical need”. If these accusations meet reality will stay unanswered, but development in regulatory activities are clearly observable and were introduced with the implementation of the new pharmacoviglance regulations (1235/2010 and 520/2012, as well as directive 2010/84/EU) and the introduction of the European E-Register. At the moment and most possibly as a next step in regulatory activities concerning approval of Orphan Drugs and ATMPs, which should be quickly accessible to patients, is the adaptive licensing process. This process of market entry is also combined with the establishment of Patient Registries[119] and the production of high quality value data in the post-authorisation phase.

Besides the requirement for at least two clinical trials as a requisite for marketing approvals[71], the activities of implementing risk management plans, risk minimisation activities and patient registries as post-authorisation activities for authorised orphan drugs and ATMPs are examples of a successful implementation of the new pharmacovigilance regulations, directives and guidelines. With the development and implementation of the European E-Register, giving standardization in data collection, validated high quality data will in future be available for different stakeholders, as well as transparency during the lifetime of the products.

8.4 New Medicinal Products push the development of regulatory activities

Having the Xigris-withdrawal in mind, the approval process of Glybera may reflect the uncertainty of the regulatory authorities and the expert committees in deciding on safety and efficacy of the first European Gene Therapeutic Product. Looking at Glybera “as a new type of medicine[120]”, the process does show several impeding facts: 1) no regulatory experience for this type of medicine, 2) a disease with a fluctuating clinical course, 3) a clinical trial and post-authorisation patient registry with limited data from a small population.

The final approval of Glybera did use a long time filled with discussions and requests from both sides, the Agency (including CHMP/PRAC and CAT) and the MAH. In his publication from 2015 Watanabe et al did concentrate on the tool of re-examination and describes the successful integration of re-examination for orphan drugs as the important step during the regulatory process. Bryant et al[121] comment in their publication on 1) finding the best primary efficacy end-point and its impact on clinical trials and 2) on the two committees that “have taken major steps by considering all data than rather a single outcome measure” as important influences in the regulatory decision process. A number of publications stated that the approval of Glybera may now open the door for approval of further gene therapeutic medicines[121, 122].

There are still unmet medical needs and the on-going development of orphan drugs and ATMPs tries to find solution to those. There is always high public and expert interest in new medicinal products, leading to broad discussions in the concerned committees as well as in the public. Experts of the specialised committees as, i.e. the PRAC and the CAT, actively take part in the development and marketing phase for orphan drugs and ATMPs and are important stakeholders on all topics concerning safety and efficacy and recommendations for regulatory activities.

The establishment of patient registries is an important practical tool to answer questions from different sources, regardless if these questions point to ADRs, different epidemiological background or just to simple all day live events. Patient registries are the instruments of choice to address all those kinds of questions.

Abbildungsverzeichnis:

Tabellenverzeichnis:

Annexes:

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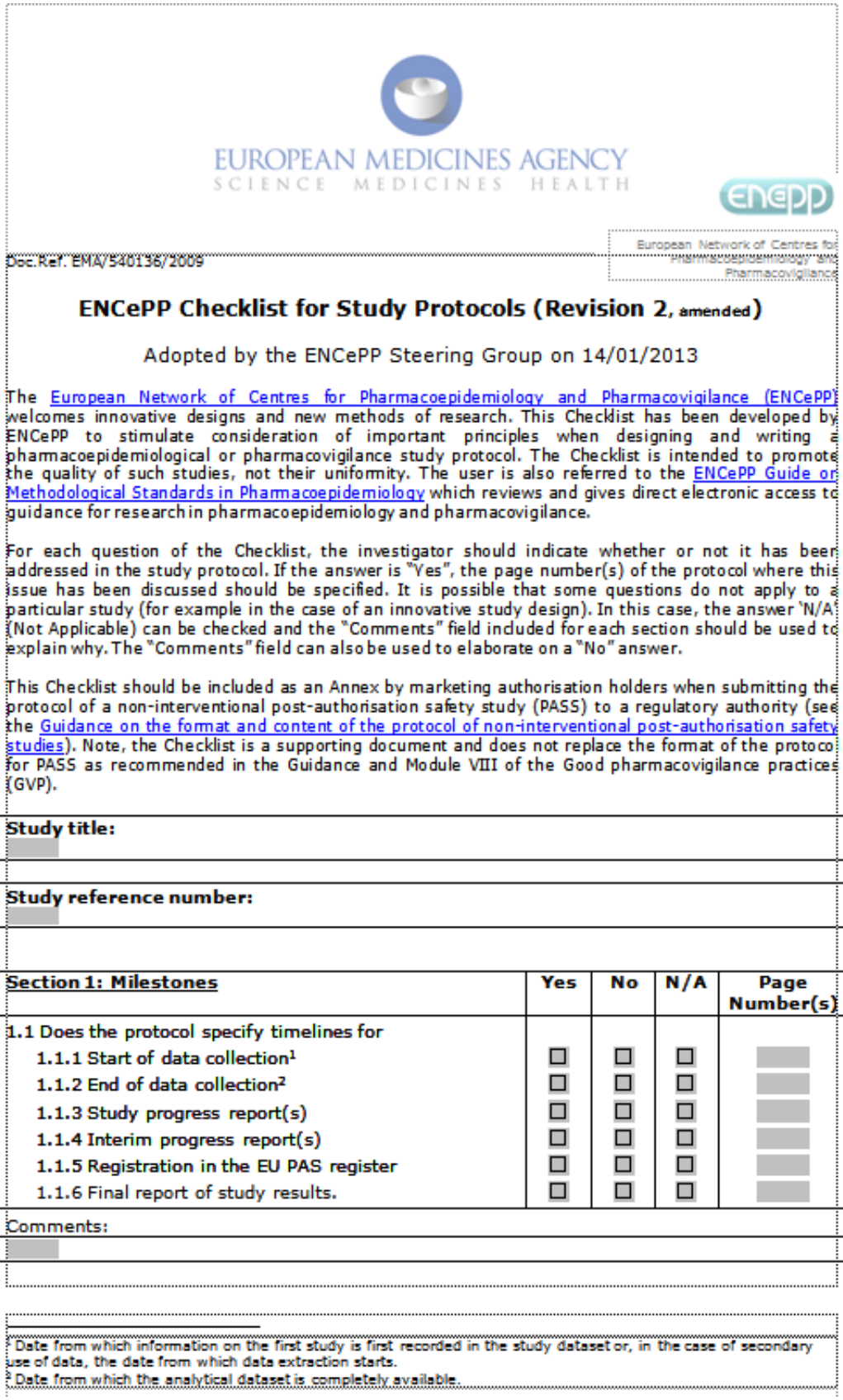
Annex I: ENCePP Checklist for Study Protocols



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Study reference number:

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☐	☐	☐	
1.1.2 End of data collection[2]	☐	☐	☐	
1.1.3 Study progress report(s)	☐	☐	☐	
1.1.4 Interim progress report(s)	☐	☐	☐	
1.1.5 Registration in the EU PAS register	☐	☐	☐	
1.1.6 Final report of study results.	☐	☐	☐	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☐	☐	☐	
2.1.2 The objective(s) of the study?	☐	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☐	☐	☐	
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☐	

Comments:

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☐	☐	☐	
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	☐	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☐	

Comments:

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☐	☐	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☐	☐	☐	
4.2.2 Age and sex?	☐	☐	☐	
4.2.3 Country of origin?	☐	☐	☐	
4.2.4 Disease/indication?	☐	☐	☐	
4.2.5 Co-morbidity?	☐	☐	☐	
4.2.6 Seasonality?	☐	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☐	

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective				

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☐	

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☐	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☐	

Comments:

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☐	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☐	

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☐	
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☐	
8.1.3 Covariates?	☐	☐	☐	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☐	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☐	
8.3 Is a coding system described for:				

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☐	

Comments:

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☐	☐	☐	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☐	☐	
10.2 Is the choice of statistical techniques described?	☐	☐	☐	
10.3 Are descriptive analyses included?	☐	☐	☐	
10.4 Are stratified analyses included?	☐	☐	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☐	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☐	☐	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☐	
11.3 Are methods of quality assurance described?	☐	☐	☐	
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☐	☐	
11.5 Is there a system in place for independent review of study results?	☐	☐	☐	

Comments:

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐ ☐	☐ ☐	☐ ☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☐	
12.3 Does the protocol address other limitations?	☐	☐	☐	

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☐	
13.3 Have data protection requirements been described?	☐	☐	☐	

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☐	☐	☐	

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☐	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☐	☐	☐	

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature:

Annex II: Protocols, abstracts and final study reports for post-authorisation safety Studies (Implementing Regulation 520/2012, Annex III)

1. ***Format of the study protocol***

1. Title**:** informative title including a commonly used term indicating the study design and the medicinal product, substance or drug class concerned, and a sub-title with a version identifier and the date of the last version.
2. Marketing authorisation holder.
3. Responsible parties including a list of all collaborating institutions and other relevant study sites.
4. Abstract: stand-alone summary of the study protocol, including the following subsections:
(a) Title with subtitles including version and date of the protocol and name and affiliation of the main author;
b) rationale and background;
(c) research question and objectives;
(d) study design;
(e) Population;
(f) Variables;
(g) data sources;
(h) Study size;
(i) data analysis;
(j) Milestones.
5. Amendments and updates: any substantial amendment and update to the study protocol after the start of data collection, including a justification for the amendment or update, the date of the change, and a reference to the section of the protocol where the change has been made.

6. Milestones: table with planned dates for the following milestones:
(a) start of data collection;
(b) end of data collection;
(c) study progress report(s) as referred to in Article 107m(5) of Directive 2001/83/EC;
(d) interim report(s) of study results, if applicable;
(e) final report of study results.

7. Rationale and background: description of the safety hazard(s), the safety profile or the risk management measures that led to the study being imposed as an obligation for a marketing authorisation.
8. Research question and objectives in accordance with the decision of the national competent authority that imposed the study as an obligation.
9. Research methods: description of the research methods, including:
(a) study design;
(b) setting: study population defined in terms of persons, place, time period, and selection criteria, including the rationale for any inclusion and exclusion criteria. Where any sampling from a source population is undertaken, a description of the source population and details of sampling methods shall be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies shall be explained;
(c) variables
(d) data sources: strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives. Where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data shall be reported. In the case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investi gators shall be described;
(e) study size: any projected study size, precision sought for study estimates and any calculation of the study size that can minimally detect a pre-specified risk with a pre-specified interpretative power;
(f) data management;
(g) data analysis;
(h) quality control;
(i) limitations of the research methods.
10. Protection of human subjects: safeguards in order to comply with national and Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies.
11. Management and reporting of adverse events/adverse reactions and other medically important events while the study is being conducted.
12. Plans for disseminating and communicating study results.
13. References.

2. ***Format of the abstract of the final study report***

1. Title, with subtitles including date of the abstract and name and affiliation of main author.
2. Keywords (not more than five keywords indicating the main study characteristics).
3. Rationale and background.
4. Research question and objectives.
5. Study design.
6. Setting.
7. Subjects and study size, including dropouts.
8. Variables and data sources.
9. Results.
10. Discussion (including, where relevant, an evaluation of the impact of study results on the risk–benefit balance of the product).
11. Marketing authorisation holder.
12. Names and affiliations of principal investigators.

3. ***Format of the final study report***

1. Title: title including a commonly used term indicating the study design; sub-titles with date of final report and name and affiliation of the main author.
2. Abstract: stand-alone summary referred to in Section 2 of this Annex.
3. Marketing authorisation holder: name and address of the marketing authorisation holder.
4. Investigators: names, titles, degrees, addresses and affiliations of the principal investigator and all co-investigators, and list of all collaborating primary institutions and other relevant study sites.
5. Milestones: dates for the following milestones:

(a) start of data collection (planned and actual dates); (b) end of data collection (planned and actual dates); (c) study progress reports;
(d) interim reports of study results, where applicable;
(e) final report of study results (planned and actual date);
(f) any other important milestone applicable to the study, including date of study registration in the electronic study register.

6. Rationale and background: description of the safety concerns that led to the study being initiated, and critical review of relevant published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill.
7. Research question and objectives.
8. Amendments and updates to the protocol: list of any substantial amendments and updates to the initial study protocol after the start of data collection, including a justification for each amendment or update.
9. Research methods

9.1. Study design: key elements of the study design and rationale for this choice.
9.2. Setting: setting, locations, and relevant dates for the study, including periods of recruitment, follow-up, and data collection. In the case of a systematic review or meta-analysis, study characteristics used as criteria for eligibility, with rationale.
9.3. Subjects: any source population and eligibility criteria for study subjects. Sources and methods for selection of participants shall be provided, including, where relevant, methods for case ascertainment, as well as number of and reasons for dropouts.
9.4. Variables: all outcomes, exposures, predictors, potential confounders, and effect modifiers, including operational definitions. Diagnostic criteria shall be provided, where applicable.
9.5. Data sources and measurement: for each variable of interest, sources of data and details of methods of assessment and measurement. If the study has used an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data shall be reported. In the case of a systematic review or meta-analysis, description of all information sources, search strategy, methods for selecting studies, methods of data extraction and any processes for obtaining or confirming data from investigators.
9.6. Bias.
9.7. Study size: study size, rationale for any study size calculation and any method for attaining projected study size.
9.8. Data transformation: transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why.
9.9. Statistical methods: description of the following items: (a) main summary measures;
(b) all statistical methods applied to the study;
(c) any methods used to examine subgroups and interactions;
(d) how missing data were addressed;
(e) any sensitivity analyses;
(f) any amendment to the plan of data analysis included in the study protocol, with rationale for the change.

9.10. Quality control: mechanisms to ensure data quality and integrity.
10. Results: comprising the following subsections:
10.1. Participants: numbers of study subjects at each stage of study. In the case of a systematic review or meta-analysis, number of studies screened, assessed for eligibility and included in the review with reasons for exclusion at each stage.
10.2. Descriptive data: characteristics of study participants, information on exposures and potential confounders and number of participants with missing data. In the case of a systematic review or meta-analysis, characteristics of each study from which data were extracted.
10.3. Outcome data: numbers of study subjects across categories of main outcomes.
10.4. Main results: unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision. Where relevant, estimates of relative risk shall be translated into absolute risk for a meaningful time period.
10.5. Other analyses.
10.6. Adverse events and adverse reactions.
11. Discussion
11.1. Key results: key results with reference to the study objectives, prior research in support of and conflicting with the findings of the completed post-authorisation safety study, and, where relevant, the impact of the results on the risk–benefit balance of the product.
11.2. Limitations: limitations of the study taking into account circumstances that may have affected the quality or integrity of the data, limitations of the study approach and methods used to address them, sources of potential bias and imprecision, and validation of the events. Both the direction and magnitude of potential biases shall be discussed.
11.3. Interpretation: interpretation of results, considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence.
11.4. Generalisability.
12. References.

Annex III Regulations and Directives, an excerpt of the legal framework for implementing patient registries

726/2004/EC, Article 3 (1) and (2):
"1. No medicinal product appearing in the Annex may be placed on the market within the Community unless a marketing authorisation has been granted by the Community in accordance with the provisions of this Regulation.
2. Any medicinal product not appearing in the Annex may be granted a marketing authorisation by the Community in accordance with the provisions of this Regulation, if:

(a) The medicinal product contains a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Community; or

(b) The applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorisation in accordance with this Regulation is in the interests of patients or animal health at Community level."

726/2004, Art 9(2):
2. Within 15 days after receipt of the opinion referred to in paragraph 1, the applicant may give written notice to the Agency that he wishes to request a re-examination of the opinion. In that case, the applicant shall forward to the Agency the detailed grounds for the request within 60 days after receipt of the opinion.

726/2004, Art 9(4), a-d:
4. If an opinion is favourable to the granting of the relevant authorisation to place the medicinal product concerned on the market, the following documents shall be annexed to the opinion:
(a) a draft summary of the product characteristics, as referred to in Article 11 of Directive 2001/83/EC;
(aa) a recommendation on the frequency of submission of periodic safety update reports;

(b) details of any conditions or restrictions which should be imposed on the supply or use of the medicinal product concerned, including the conditions under which the medicinal product may be made available to patients, in accordance with the criteria laid down in Title VI of Directive 2001/83/EC;

(c) details of any recommended conditions or restrictions with regard to the safe and effective use of the medicinal product;

(ca) details of any recommended measures for ensuring the safe use of the medicinal product to be included in the risk management system;

(cb) if appropriate, details of any recommended obligation to conduct post-authorisation safety studies or to comply with obligations on the recording or reporting of suspected adverse reactions, which are stricter than, those referred to in Chapter 3;

(cc) if appropriate, details of any recommended obligation to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. Such an obligation to conduct such studies shall be based on the delegated acts adopted pursuant to Article 10b while taking into account the scientific guidance referred to in Article 108a of Directive 2001/83/EC;

(d) the draft text of the labelling and package leaflet proposed by the applicant, presented in accordance with Title V of Directive 2001/83/EC;

726/2004, Art 10, amended by Regulation 1235/2010:
1. Within 15 days after receipt of the opinion referred to in Article 5(2), the Commission shall prepare a draft of the decision to be taken in respect of the application.

Where a draft decision envisages the granting of a marketing authorisation, it shall include or make reference to the documents mentioned in points (a) to (d) of Article 9(4).

Where a draft decision envisages the granting of a marketing authorisation subject to the conditions referred to in points (c), (ca), (cb), or (cc) of Article 9(4), it shall lay down deadlines for the fulfilment of the conditions, where necessary.

Where the draft decision differs from the opinion of the Agency, the Commission shall attach a detailed explanation of the reasons for the differences.

The draft decision shall be forwarded to Member States and the applicant.

2.The Commission shall take a final decision in accordance with, and within 15 days after the end of, the procedure referred to in Article 87(3).

726/2004 Article 10a, as amended by Regulation 1235/2010:
1. After the granting of a marketing authorisation, the Agency may impose an obligation on the marketing authorisation holder:
1. (a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the Agency shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study;
2. (b) to conduct a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorisation efficacy study shall be based on the delegated acts adopted pursuant to Article 10b while taking into account the scientific guidance referred to in Article 108a of Directive 2001/83/EC.
The imposition of such an obligation shall be duly justified, notified in writing, and shall include the objectives and timeframe for submission and conduct of the study.

2. The Agency shall provide the marketing authorisation holder with an opportunity to present written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.

3. On the basis of the written observations submitted by the marketing authorisation holder, and of the opinion of the Agency, the Commission shall withdraw or confirm the obligation. Where the Commission confirms the obligation, the marketing authorisation shall be varied to include the obligation as a condition of the marketing authorisation and the risk management system shall be updated accordingly.

726/2004, Article 14 (7):
Following consultation with the applicant, an authorisation maybe granted subject to certain specific obligations, to be reviewed annually by the Agency. The list of these obligations shall be made publicly accessible. By way of derogation from paragraph 1, such authorisation shall be valid for one year, on a renewable basis.

726/2004, Article 14 (8):
In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted subject to certain conditions, in particular relating to the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. The marketing authorisation may be granted only when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I to Directive 2001/83/EC. Continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions.

726/2004, Article 14 (9):
When an application is submitted for a marketing authorisation in respect of medicinal products for human use, which are of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure. The request shall be duly substantiated.
If the Committee for Medicinal Products for Human Use accepts the request, the time-limit laid down in Article 6(3), first subparagraph, shall be reduced to 150 days.

726/2004, Article 23:
1. The Agency shall, in collaboration with the Member States, set up, maintain and make public a list of medicinal products that are subject to additional monitoring.
That list shall include the names and active substances of:
(a) Medicinal products authorised in the Union that contain a new active substance, which, on 1 January 2011, was not contained in any medicinal product authorised in the Union;
(b) Any biological medicinal product not covered by point (a) that was authorised after 1 January 2011;
(c) Medicinal products that are authorised pursuant to this Regulation, subject to the conditions referred to in point (cb) of Article 9(4), point (a) of the first subparagraph of Article 10a(1) or Article 14(7) or (8);
(d) Medicinal products that are authorised pursuant to Directive 2001/83/EC, subject to the conditions referred to in points (b) and (c) of the first paragraph of Article 21a, Article 22, or point (a) of the first subparagraph of Article 22a(1) thereof.

1a. At the request of the Commission, following consultation with the Pharmacovigilance Risk Assessment Committee, medicinal products that are authorised pursuant to this Regulation, subject to the conditions referred to in points (c), (ca) or (cc) of Article 9(4), point (b) of the first subparagraph of Article 10a(1) or Article 21(2), may also be included in the list referred to in paragraph 1 of this Article.
At the request of a national competent authority, following consultation with the Pharmacovigilance Risk Assessment Committee, medicinal products that are authorised pursuant to Directive 2001/83/EC, subject to the conditions referred to in points (a), (d), (e) or (f) of the first paragraph of Article 21a, point (b) of the first subparagraph of Article 22a(1) or Article 104a(2) thereof, may also be included in the list referred to in paragraph 1 of this Article.

2. The list referred to in paragraph 1 shall include an electronic link to the product information and to the summary of the risk management plan.

3. In the cases referred to in points (a) and (b) of paragraph 1 of this Article, the Agency shall remove a medicinal product from the list five years after the Union reference date referred to in Article 107c(5) of Directive 2001/83/EC.
In the cases referred to in points (c) and (d) of paragraph 1 and in paragraph 1a of this Article, the Agency shall remove a medicinal product from the list once the conditions have been fulfilled.

4. For medicinal products included in the list referred to in paragraph 1, the summary of product characteristics and the package leaflet shall include the statement 'This medicinal product is subject to additional monitoring'. That statement shall be preceded by a black symbol which shall be selected by the Commission by 2 July 2013, following a recommendation of the Pharmacovigilance Risk Assessment Committee, and shall be followed by an appropriate standardised explanatory sentence.

4a. By 5 June 2018, the Commission shall present to the European Parliament and the Council a report on the use of the list referred to in paragraph 1 based on the experience and data provided by the Member States and the Agency.

The Commission shall, if appropriate, on the basis of that report, and after consultation with the Member States and other appropriate stakeholders, present a proposal in order to adjust the provisions relating to the list referred to in paragraph 1.

726/2004, Article 26:
The Agency, in consultation with Member States and the Commission, shall set up a data-processing network for the rapid transmission of information to the competent Community authorities in the event of an alert relating to faulty manufacture, serious adverse reactions and other pharamacovigilance data regarding medicinal products authorised in accordance with Article 6 of Directive 2001/83/EC. Such data shall be made publicly accessible, if relevant, after evaluation.
For a period of five years following the initial placing on the market in the Community, the Agency may request that the marketing authorisation holder arrange for specific pharmacovigilance data to be collected from targeted groups of patients. The Agency shall state the reasons for the request. The marketing authorisation holder shall collate and assess the data collected and submit it to the Agency for evaluation.

Directive 2001/83, Article 8 (3):
1. In order to obtain an authorization to place a medicinal product on the market regardless of the procedure established by Regulation (EEC) No 2309/93, an application shall be made to the competent authority of the Member State concerned.

2. A marketing authorization may only be granted to an applicant established in the Community.

3. The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:
(a) Name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer.
(b) Name of the medicinal product.
(c) Qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its international non-proprietary name (INN) recommended by the WHO, where an INN for the medicinal product exists, or a reference to the relevant chemical name.
(ca) Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case- by-case basis, specific arrangements to limit it shall be envisaged.
(d) Description of the manufacturing method.
(e) Therapeutic indications, contra-indications and adverse reactions.
(f) Posology, pharmaceutical form, method and route of administration and expected shelf life.
(g) Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.
(h) Description of the control methods employed by the manufacturer.
(ha) A written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practice by conducting audits, in accordance with point (f) of Article 46. The written confirmation shall contain a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles and guidelines of good manufacturing practice.
(i) Results of:
— pharmaceutical (physico-chemical, biological or microbiological) tests,
— pre-clinical (toxicological and pharmacological) tests,
— clinical trials.

ia) A summary of the applicant's pharmacovigilance system which shall include the following elements:

- proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance,
- the Member States in which the qualified person resides and carries out his/her tasks,
- the contact details of the qualified person,
- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX,
- a reference to the location where the pharmacovigilance system master file for the medicinal product is kept.

(iaa) The risk management plan describing the risk management system, which the applicant will introduce for the medicinal product concerned, together with a summary thereof.

Directive 2010/84: Article 21a:
In addition to the provisions laid down in Article 19, a marketing authorisation for a medicinal product may be granted subject to one or more of the following conditions:

(a) to take certain measures for ensuring the safe use of the medicinal product to be included in the risk management system;

(b) to conduct post-authorisation safety studies;

(c) to comply with obligations on the recording or reporting of suspected adverse reactions which are stricter than those referred to in Title IX;

(d) any other conditions or restrictions with regard to the safe and effective use of the medicinal product;

(e) the existence of an adequate pharmacovigilance system;

(f) to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. Such an obligation to conduct such studies shall be based on the delegated acts adopted pursuant to Article 22b while taking into account the scientific guidance referred to in Article 108a.

The marketing authorisation shall lay down deadlines for the fulfilment of these conditions where necessary.'

Directive 2001/83/EC, Article 22:
In exceptional circumstances and following consultation with the applicant, the authorisation may be granted subject to a requirement for the applicant to meet certain conditions, in particular concerning the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken.

This authorisation may be granted only for objective, verifiable reasons and must be based on one of the grounds set out in Annex I.

Continuation of the authorisation shall be linked to the annual reassessment of these conditions. The list of these conditions shall be made publicly accessible without delay, together with deadlines and dates of fulfilment.

Directive 2001/83/EC, Article 22a, inserted after amendment by 2010/84/EC:

1. After the granting of a marketing authorisation, the national competent authority may impose an obligation on the marketing authorisation holder:

1. (a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the national competent authority shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study;
2. (b) to conduct a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorisation efficacy study shall be based on the delegated acts adopted pursuant to Article 22b while taking into account the scientific guidance referred to in Article 108a.

The imposition of such an obligation shall be duly justified, notified in writing, and shall include the objectives and timeframe for submission and conduct of the study.

Directive 2001/83/EC, Article 22b, inserted after amendment by 2010/84/EC:

1. In order to determine the situations in which post-authorisation efficacy studies may be required under Articles 21a and 22a of this Directive, the Commission may adopt, by means of delegated acts in accordance with Article 121a, and subject to the conditions of Articles 121b and 121c, measures supplementing the provisions in Articles 21a and 22a.

2. When adopting such delegated acts, the Commission shall act in accordance with the provisions of this Directive.

Directive 2001/83/EC, Annex I, Part II.6 (now laid down in 2003/63/EC):

3. "Documentation for Applications in Exceptional Circumstances

When, as provided for in Article 22, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

. the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or

. in the present state of scientific knowledge, comprehensive information cannot be provided, or

. it would be contrary to generally accepted principles of medical ethics to collect such information, marketing authorisation may be granted subject to certain specific obligations.

These obligations may include the following:

. the applicant shall complete an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/ risk profile,

. the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorised person,

. the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

Directive 2001/83/EC, Article 107m:

1. This Chapter applies to non-interventional post-authorisation safety studies which are initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed in accordance with Articles 21a or 22a, and which involve the collection of safety data from patients or healthcare professionals.

2. This Chapter is without prejudice to national and Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies.

3. The studies shall not be performed where the act of conducting the study promotes the use of a medicinal product.

4. Payments to healthcare professionals for participating in non-interventional post-authorisation safety studies shall be restricted to the compensation for time and expenses incurred.

5. The national competent authority may require the marketing authorisation holder to submit the protocol and the progress reports to the competent authorities of the Member States in which the study is conducted.

6. The marketing authorisation holder shall send the final report to the competent authorities of the Member States in which the study was conducted within 12 months of the end of data collection.

7. While a study is being conducted, the marketing authorisation holder shall monitor the data generated and consider its implications for the risk-benefit balance of the medicinal product concerned.
Any new information, which might influence the evaluation of the risk-benefit balance of the medicinal product shall be communicated to the competent authorities of the Member State in which the medicinal product has been authorised in accordance with Article 23.
The obligation laid down in the second subparagraph is without prejudice to the information on the results of studies that the marketing authorisation holder shall make available by means of the periodic safety update reports as laid down in Article 107b.

8. Articles 107n to 107q shall apply exclusively to studies referred to in paragraph 1, which are conducted pursuant to an obligation imposed in accordance with Articles 21a or 22a.

Directive 2001/83/EC, Article 107n:

1. Before a study is conducted, the marketing authorisation holder shall submit a draft protocol to the Pharmacovigilance Risk Assessment Committee, except for studies to be conducted in only one Member State that requests the study according to Article 22a. For such studies, the marketing authorisation holder shall submit a draft protocol to the national competent authority of the Member State in which the study is conducted.

2. Within 60 days of the submission of the draft protocol the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall issue:
(a) a letter endorsing the draft protocol;
(b) a letter of objection, which shall set out in detail the grounds for the objection, in any of the following cases:
(i) it considers that the conduct of the study promotes the use of a medicinal product;
(ii) it considers that the design of the study does not fulfil the study objectives; or

(c) a letter notifying the marketing authorisation holder that the study is a clinical trial falling under the scope of Directive 2001/20/EC.

3. The study may commence only when the written endorsement from the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, has been issued.

Where a letter of endorsement as referred to in paragraph 2(a) has been issued, the marketing authorisation holder shall forward the protocol to the competent authorities of the Member States in which the study is to be conducted and may thereafter commence the study according to the endorsed protocol.

Directive 2001/83/EC, Article 107o:
After a study has been commenced, any substantial amendments to the protocol shall be submitted, before their implementation, to the national competent authority or to the Pharmacovigilance Risk Assessment Committee, as appropriate. The national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall assess the amendments and inform the marketing authorisation holder of its endorsement or objection. Where applicable, the marketing auth orisation holder shall inform Member States in which the study is conducted.

Directive 2001/83/EC, Article 107p:
1. Upon completion of the study, a final study report shall be submitted to the national competent authority or the Pharmacovigilance Risk Assessment Committee within 12 months of the end of data collection unless a written waiver has been granted by the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate.

2. The marketing authorisation holder shall evaluate whether the results of the study have an impact on the marketing authorisation and shall, if necessary, submit to the national competent authorities an application to vary the marketing authorisation.

3. Together with the final study report, the marketing authorisation holder shall electronically submit an abstract of the study results to the national competent authority or the Pharmacovigilance Risk Assessment Committee.

Directive 2001/83/EC, Article 107q:

1. Based on the results of the study and after consultation of the marketing authorisation holder, the Pharmacovigilance Risk Assessment Committee may make recommendations concerning the marketing authorisation, stating the reasons on which they are based. The recommendations shall mention the divergent positions and the grounds on which they are based.

2. When recommendations for the variation, suspension or revocation of the marketing authorisation are made for a medicinal product authorised by the Member States pursuant to this Directive, the Member States represented within the coordination group shall agree a position on the matter taking into account the recommendation referred to in paragraph 1 and including a timetable for the implementation of the agreed position.

If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to vary, suspend or revoke the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

In the event that a variation is agreed upon, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a variation, including an updated summary of product characteristics and package leaflet within the determined timetable for implementation.

The agreement shall be made public on the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission, which shall apply the procedure laid down in Articles 33 and 34.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of Member States differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

Directive 2001/83/EC, Article 108a:
In order to facilitate the performance of pharmacovigilance activities within the Union, the Agency shall, in cooperation with competent authorities and other interested parties, draw up:

(a) guidance on good pharmacovigilance practices for both competent authorities and marketing authorisation holders;

(b) scientific guidance on post-authorisation efficacy studies.

Implementing Regulation 520/2012, Artikel 36:

Scope
1. This chapter applies to non-interventional post-authorisation safety studies initiated, managed or financed by a marketing authorisation holder under obligations imposed by a national competent authority, the Agency or the Commission in accordance with Articles 21a and 22a of Directive 2001/83/EC and Articles 10 and 10a of Regulation (EC) No 726/2004.

2. The marketing authorisation holder shall submit the study protocol, the abstract of the final study report and the final study report which have been provided in accordance with Articles 107n and 107p of Directive 2001/83/EC in English except for studies to be conducted in only one Member State that requests the study according to Article 22a of Directive 2001/83/EC. For the latter studies the marketing authorisation holder shall provide an English translation of the title and abstract of the study protocol as well as an English translation of the abstract of the final study report.

3. The marketing authorisation holder shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected. The marketing authorisation holder shall ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

4. The Agency may publish appropriate templates for the protocol, abstract and final study report.

Implementing Regulation 520/2012, Artikel 37:

Definitions
For the purposes of this chapter, the following definitions shall apply:
1. (1) 'Start of data collection' means the date from which information on the first study subject is first recorded in the study dataset or, in the case of the secondary use of data, the date from which data extraction starts;
2. (2) 'End of data collection' means the date from which the analytical dataset is completely available.

Implementing Regulation 520/2012, Artikel 38:
Format of post-authorisation safety studies
Protocols, abstracts and final study reports for non-interventional post-authorisation safety studies shall be submitted in the format set out in Annex III.

Implementing Regulation 520/2012, Artikel 40:
Transitional provisions
1. The obligation on the part of marketing authorisation holders, national competent authorities and the Agency to use the terminology provided for in points (c) to (g) of Article 25 shall apply from 1 July 2016.
2. Article26 (2) shall apply from 1 July 2016.
3. The obligation on the part of the marketing authorisation holder to comply with the format and content as provided for in Articles 29 to 38 shall apply from 10 January 2013.

Directive 2011/24, Article 12: European reference networks
1. The Commission shall support Member States in the development of European reference networks between healthcare providers and centres of expertise in the Member States, in particular in the area of rare diseases in. The networks shall be based on voluntary participation by its members, which shall participate and contribute to the networks' activities in accordance with the legislation of the Member State where the members are established and shall at all times be open to new healthcare providers which might wish to join them, provided that such healthcare providers fulfil all the required conditions and criteria referred to in paragraph 4.

2. European reference networks shall have at least three of the following objectives:

(a) to help realise the potential of European cooperation regarding highly specialised healthcare for patients and for healthcare systems by exploiting innovations in medical science and health technologies;
(b) to contribute to the pooling of knowledge regarding sickness prevention;
(c) to facilitate improvements in diagnosis and the delivery of high-quality, accessible and cost-effective healthcare for all patients with a medical condition requiring a particular concentration of expertise in medical domains where expertise is rare;
(d) to maximise the cost-effective use of resources by concentrating them where appropriate;
(e) to reinforce research, epidemiological surveillance like registries and provide training for health professionals;
(f) to facilitate mobility of expertise, virtually or physically, and to develop, share and spread information, knowledge and best practice and to foster developments of the diagnosis and treatment of rare diseases, within and outside the networks;
(g) to encourage the development of quality and safety benchmarks and to help develop and spread best practice within and outside the network;
(h) to help Member States with an insufficient number of patients with a particular medical condition or lacking technology or expertise to provide highly specialised services of high quality.
3. Member States are encouraged to facilitate the development of the European reference networks:
(a) by connecting appropriate healthcare providers and centres of expertise throughout their national territory and ensuring the dissemination of information towards appropriate healthcare providers and centres of expertise throughout their national territory;
(b) by fostering the participation of healthcare providers and centres of expertise in the European reference networks.

4. For the purposes of paragraph 1, the Commission shall:
(a) adopt a list of specific criteria and conditions that the European reference networks must fulfil and the conditions and criteria required from healthcare providers wishing to join the European reference network. These criteria and conditions shall ensure, inter alia, that European reference networks:
(i) have knowledge and expertise to diagnose, follow-up and manage patients with evidence of good outcomes, as far as applicable;
(ii) follow a multi-disciplinary approach;
(iii) offer a high level of expertise and have the capacity to produce good practice guidelines and to implement outcome measures and quality control;
(iv) make a contribution to research;
(v) organise teaching and training activities; and
(vi) collaborate closely with other centres of expertise and networks at national and international level;
b) develop and publish criteria for establishing and evaluating European reference networks;
c) facilitate the exchange of information and expertise in relation to the establishment of European reference networks and their evaluation.

5. The Commission shall adopt the measures referred to in paragraph 4(a) by means of delegated acts in accordance with Article 17 and subject to the conditions of Articles 18 and 19. The measures referred to in points (b) and (c) of paragraph 4 shall be adopted in accordance with the regulatory procedure referred to in Article 16(2).

6. Measures adopted pursuant to this Article shall not harmonise any laws or regulations of the Member States and shall fully respect the responsibilities of the Member States for the organisation and delivery of health services and medical care.

Directive 2010/20/EC, Article 23 (former 16, amended):
1. After a marketing authorisation has been granted, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h), take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

Those changes shall be subject to the approval of the competent authority of the Member State concerned.

2. The marketing authorisation holder shall forthwith provide the national competent authority with any new information which might entail the amendment of the particulars or documents referred to in Article 8(3), Articles 10, 10a, 10b and 11, or Article 32(5), or Annex I.

In particular, the marketing authorisation holder shall forthwith inform the national competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information, which might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.

3. The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.

4. In order to be able to continuously assess the risk- benefit balance, the national competent authority may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable. The marketing authorisation holder shall answer fully and promptly any such request.

The national competent authority may at any time ask the marketing authorisation holder to submit a copy of the pharmacovigilance system master file. The marketing authorisation holder shall submit the copy at the latest 7 days after receipt of the request.'

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

Bonn, den

Dr. Barbara Siebertz

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