

**Approval of a biological medicinal product
within the Mutual Recognition Procedure (RMS: Germany) –
regulatory strategies and potential challenges
from a consulting company's point of view
with regard to current pharmaceutical legislation**

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List of Abbreviations

Abbreviation	Full Term
AIDS	Acquired Immunodeficiency Syndrome
AMG	Arzneimittelgesetz (German Drug Law)
AR	Assessment Report
ASMF	Active Substance Master File
AT	Austria
ATMP	Advanced Therapy Medicinal Product
BE	Belgium
BE/BA	Bioequivalence/Bioavailability
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BMWP	Biosimilar Medicinal Products Working Party
BVL	Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (Federal Office of Consumer Protection and Food Safety)
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - human
CMS	Concerned Member State
COMP	Committee for Orphan Medicinal Products
CP	Centralised Procedure
CRD	Common Renewal Date
CRO	Clinical Research Organisation
CT	Clinical Trial
CTA	Clinical Trial Application
CTD	Common Technical Document
CY	Cyprus
CZ	Czech Republic
DCP	Decentralised Procedure
DK	Denmark
DNA	Deoxyribonucleic Acid
DRA	Drug Regulatory Affairs
DRAM	Drug Regulatory Affairs Manager
EC	European Commission
eCTD	electronic Common Technical Document

Abbreviation	Full Term
EDQM	European Directorate for Quality of Medicines
EEA	European Economic Area
EFTA	European Free Trade Association
EMA	European Medicines Agency
EU	European Union
FI	Finland
FLI	Friedrich-Loeffler-Institut (Friedrich-Loeffler Institute)
FR	France
FUM	Follow-up Measure
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HMA	Heads of Medicines Agencies
IMPD	Investigational Medicinal Product Dossier
LOC	Local Operating Company
LOQ	List of Questions
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency, UK
MRP	Mutual Recognition Procedure
MS	Member State
NCA	National Competent Authority
NO	Norway
NP	National Procedure
OCABR	Official Control Authority Batch Release
OMCL	Official Medicine Control Laboratories
PDCO	Paediatric Committee
PEI	Paul-Ehrlich-Institut (Paul-Ehrlich Institute)
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PL	Package Leaflet Poland

Abbreviation	Full Term
PMF	Plasma Master File
PSRPH	Potential Serious Risk to Public Health
PSUR	Periodic Safety Update Report
PT	Portugal
QPPV	Qualified Person for Pharmacovigilance
QRD	Quality Review of Documents
RA	Regulatory Affairs
RKI	Robert Koch-Institut (Robert Koch Institute)
RMP	Risk Management Plan
RMS	Reference Member State
RUT	Readability User Testing
SAWP	Scientific Advice Working Party
SE	Sweden
SME	Micro, Small and Medium-sized Enterprise
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
STIKO	Ständige Impfkommision (German Standing Vaccination Committee)
TAV	Therapieallergene-Verordnung (Therapy Allergens Ordinance)
TIGes	Telematic Implementation Group – electronic submission
UK	United Kingdom
USR	Urgent Safety Restriction
VAMF	Vaccine Antigen Master File
WHO	World Health Organisation

1. Introduction

Biological medicinal products, also referred to as biomedicinal products or biologicals, contain an active substance that is produced by or extracted from a biological source. The definition is given in Part I of Annex I of Directive 2001/83/EC¹ and is discussed in section 2.1.1 “Definition of a biological medicinal product” of this master thesis. Immunological medicinal products, such as allergen products fall under this definition and play an important role in the therapy and diagnostics of several allergic diseases.

For biological medicinal products special legal rules apply. This concerns amongst others the approval procedure including approval of clinical studies, the manufacturing authorisation, the batch release procedure and variations of the Marketing Authorisation dossier. Special legal rules are based on:

- Biological reasons
- Public health reasons

The quality and safety of a biological medicinal product is defined by the manufacturing process and can be affected by minor changes in this process. Therefore, the development of the manufacturing process and the control of the resulting product with physico-chemical-biological methods are of great importance. This complexity has to be considered as the main difference to chemically synthesised medicinal products.²

An example of a public health reason for the requirement of special legal rules for biological medicinal products is the need for vaccines. The development and control of vaccines are aspects of public health. In Germany, the German Standing Vaccination Committee (Ständige Impfkommision, STIKO) is the federal commission for vaccination issues. The Robert Koch Institute (RKI), based in Berlin, publishes an immunisation schedule developed by the STIKO annually. It includes immunisation recommendations with justifications. These immunisations are paid for by the statutory health insurance companies to ensure the protection of public health.³

To make biological medicinal products available for as many patients as possible, in particular the Centralised Procedure (CP) is available. It leads to one Marketing Authorisation for the medicinal product concerned that is valid throughout the entire European Union. All

medicinal products that fall under the Annex of Commission Regulation (EC) No 726/2004 are mandatory to be authorised by the Community via the Centralised Procedure. These are as follows:⁴

- Medicinal products derived from biotechnological processes, for example using recombinant Deoxyribonucleic Acid (DNA)
- Advanced Therapy Medicinal Products (ATMPs) using gene therapy, somatic cell therapy or tissue engineering
- Medicinal products containing a new active substance with the indication for treatment of Acquired Immunodeficiency Syndrome (AIDS), cancer, neurodegenerative disorders like Parkinson's, diabetes, auto-immune diseases or other immune dysfunctions, viral diseases
- Medicinal products used for rare diseases (officially designated by the Committee for Orphan Medicinal Products, COMP, as orphan medicinal products)

However, biological medicinal products that do not fall under the above-mentioned Annex can also be approved by a purely National Procedure (NP), Mutual Recognition Procedure (MRP) or a Decentralised Procedure (DCP). The Mutual Recognition Procedure is described in detail in section 2.2.2 “Characteristics of the MRP” and is the focus in this master thesis.

In Germany, a National Competent Authority (NCA) exists that is a specialist for biological medicinal products: the Paul-Ehrlich Institute (PEI). The PEI, founded in 1896 and based in Langen, carries out its own research and provides its expertise on an international level.^{5, 6} In section 2.1.3 “Role of the Paul-Ehrlich Institute” further details are given.

The aim of this master thesis is to examine how a biological medicinal product can be approved during a Mutual Recognition Procedure with Germany as Reference Member State (RMS). Within the framework of a fictional case study and using the example of an allergen product, regulatory strategies and potential challenges during an MRP in general and with a biological medicinal product in particular will be pointed out.

Overall, a guide will be provided to show how to manage such a large project successfully and efficiently from a consulting company's point of view. Focus is on the planning and realisation of the procedure as well as on the requirements following receipt of the approval.

The role of a consulting company in this context, acting on behalf of the applicant, with its tasks and limits will be outlined.

In this master thesis, attention is paid to current literature concerning Drug Regulatory Affairs (DRA) and this literature is discussed with relation to the case study. In addition, current pharmaceutical legislation, such as the new Variation Regulation, Commission Regulation (EC) No 1234/2008, is taken into account.

Due to the complexity of the chosen topic, focus is based on the case study, which is described in section 3. "Case study description". Due to its expertise with biological medicinal products, interaction with one National Competent Authority, the Paul-Ehrlich Institute, is discussed in detail. National requirements of other countries in their role as Concerned Member States (CMSs) are explained only exemplarily. Focus within the biological medicinal products is laid on allergen products.

The present master thesis is structured as follows:

- General aspects and definitions with regard to the topic
- Description of the case study
- Examination of the topic with regard to the case study
- Final discussion, conclusion and outlook

2. General aspects of approving a biological medicinal product within the MRP

2.1 Biological medicinal products

2.1.1 Definition of a biological medicinal product

For human medicinal products to be authorised via the Mutual Recognition Procedure (MRP) and the Decentralised Procedure (DCP), the legal provisions are laid down in Directive 2001/83/EC as amended. For medicinal products to be authorised via the Centralised Procedure (CP), the legal provisions are laid down in Regulation EC/726/2004. However, all definitions laid down in Article 1 of Directive 2001/83/EC, such as of an immunological medicinal product, also apply for Regulation EC/726/2004.⁷

A biological medicinal product is not defined in the Directive 2001/83/EC itself. The definition of a biological medicinal product appears in its Annex, namely in section 3.2.1.1., Part I of Annex I. This current Annex was published with Directive 2003/63/EC of 25 June 2003 and provides the following definition:¹

“A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.”

Therefore, a biological medicinal product is defined by three parameters:

- What it is (product with a biological substance as active substance)
- Its source (produced by or extracted from a biological source)
- The need for special requirements to characterise and determine its quality (a combination of physico-chemical and biological testing as well as the production process and its control is necessary)

According to the above-mentioned Annex, the following shall be considered as biological medicinal products:¹

- Immunological medicinal products (defined in Article 1 paragraph 4)
- Medicinal products derived from human blood and human plasma (defined in Article 1 paragraphs 4 and 10)
- Medicinal products developed by means of one of the following biotechnological processes (according to the Annex of Regulation EC/726/2004):
 - Recombinant DNA technology
 - Controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells
 - Hybridoma and monoclonal antibody methods
- Advanced Therapy Medicinal Products (defined in Part IV of Annex I)

In compliance with this definition, the Heads of Medicines Agencies (HMA) published a Questions and Answers document regarding “Guidance for applicants on biologicals”. According to this document, the following shall be considered as biological medicinal products:⁸

- Recombinant proteins
- Monoclonal antibodies
- Blood products
- Immunological medicinal products
- Advanced technology products

In the case study of this master thesis, the approval of an allergen product is examined. Immunological medicinal products, such as allergen products, are directly defined within Directive 2001/83/EC as follows (Article 1 paragraph 4):

“Any medicinal product consisting of vaccines, toxins, serums or allergen products”, in which allergen products are considered as “any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent”.

The above-mentioned Directive was transposed into national law in Germany by amending the German Drug Law (Arzneimittelgesetz, AMG). The definition of an allergen product is given in section 4 para 5 AMG. It differentiates between:⁹

- Test allergens (for the diagnosis of specific antitoxins or protective agents)
- Therapy allergens (to achieve an antigen-specific reduction in the case of a specific immunological over-sensitivity)

2.1.2 Special regulatory requirements for biological medicinal products

In contrast to chemically synthesised medicinal products with a known chemical structure, biological medicinal products are often complex mixtures containing complex molecular structures that cannot easily be identified or fully characterised. Molecular complexity can be due to:¹⁰

- Primary to quaternary molecular structure
- Post-translational modifications, such as the nature of glycosylation
- N/C terminal modifications

Biological medicinal products that are obtained in living systems have a very complex manufacturing process. Every change in this process can lead to changes in the protein glycosylation or folding which cannot always be identified by physico-chemical methods.¹¹

This means that the manufacturing process itself defines the final product quality. With regard to Regulatory Affairs, the resulting consequences for biological medicinal products from that are as follows:

- Comprehensive information concerning quality and safety for approval is required. Therefore, bibliographic applications according to Article 10a of Directive 2001/83/EC are usually not possible
- The use of the Active Substance Master File (ASMF) concept according to Directive 2001/83/EC is not applicable, because the applicant cannot take full responsibility for the medicinal product without having access to all the quality related information¹²
- The introduction of a concept of similar biological medicinal products (also called biosimilars) as defined in Article 10(4) of Directive 2001/83/EC is necessary. The problems associated with biosimilars due to the limited possibility to show the similar nature of the concerned products must be taken into consideration¹³
- Specific conditions have to be fulfilled and specific documentation has to be supplied for post-approval changes¹⁴

Biological medicinal products are indicated for the treatment of many diseases and have a great potential for patients and pharmaceutical industries. Biologicals like Advanced Therapy Medicinal Products may, in the future, offer revolutionary treatments for diseases, such as Alzheimer's^{15, 16}. To make these medicinal products available to patients and healthcare professionals all over the EU and to gain as much data as possible, it is compulsory to authorise them via the Centralised Procedure. The following biological medicinal products fall within the Annex of Regulation EC/726/2004 "Medicinal products to be authorised by the Community":

- Medicinal products derived from biotechnological processes, for example using recombinant DNA
- Advanced Therapy Medicinal Products using gene therapy, somatic cell therapy or tissue engineering

- Medicinal products containing a new active substance with the indication for treatment of AIDS, cancer, neurodegenerative disorders like Parkinson's, diabetes, auto-immune diseases or other immune dysfunctions, viral diseases
- Medicinal products used for rare diseases

All other biological medicinal products can be authorised by a purely National Procedure (NP), Mutual Recognition Procedure (MRP) or a Decentralised Procedure (DCP).

Several guidelines with regard to biological medicinal products are available on the European Medicines Agency (EMA) website¹⁷ for applicants/Marketing Authorisation Holders (MAHs) and will be referenced in this master thesis as appropriate.

2.1.3 Role of the Paul-Ehrlich Institute

In Germany, there are four National Competent Authorities (NCAs) for the approval of medicinal products:

- Federal Institute for Drugs and Medical Devices
(Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM), based in Bonn
- Paul-Ehrlich Institute (PEI), based in Langen near Frankfurt
- Friedrich-Loeffler Institute (FLI), based in Greifswald - Island of Riems
- Federal Office of Consumer Protection and Food Safety
(Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, BVL),
based in Berlin and Braunschweig

The PEI concentrates on biological medicinal products, such as allergens, vaccines and blood preparations. The FLI focuses on immunological veterinary medicinal products against exotic epizootics. The BVL focuses on veterinary medicinal products not covered by the PEI or the FLI. The BfArM automatically has the responsibility for all other medicinal products not covered by one of these three NCAs (exclusion principle).

In this master thesis, the role of the PEI acting as the Reference Member State (RMS) in a Mutual Recognition Procedure (MRP) will be examined.

According to section 77 AMG, the PEI is competent for “*sera, vaccines, blood preparations, bone marrow preparations, tissue preparations, tissues, allergens, advanced therapy medicinal products, xenogenic medicinal products and blood components manufactured using genetic engineering*”⁹. It was founded in 1896 in Berlin as a research organisation and as an institution for the control of medicines.⁶

The duties of the PEI in its present form are based on the “Act on the Establishment of a Federal Agency for Sera and Vaccines” (Gesetz über die Errichtung eines Bundesamtes für Sera und Impfstoffe) of 7 July 1972, as amended¹⁸. According to this Act and within the scope of above-mentioned biologicals, the duties of the PEI are as follows:

- Approval of Clinical Trials (CTs)
- Granting of Marketing Authorisations (MAs) for the Federal Republic of Germany
- Carrying out or participating in inspections within the scope of Marketing Authorisation Applications (MAAs) or Clinical Trial Applications (CTAs)
- Official testing and release of batches
- Processing of applications regarding post-approval changes
- Collection and evaluation of adverse reaction reports and taking appropriate measures
- Research and advice on scientific or procedural questions

Due to this combination of drug regulatory activities, test laboratories and research, the PEI has established itself as a leading institute in Europe. In addition, the PEI’s expertise is well respected on an international level. Since 2005 it is a World Health Organisation (WHO) collaborating centre for quality assurance of blood products and in-vitro diagnostic devices^{19,20}. Within a Decentralised Procedure and including all its National Competent Authorities, Germany is the most chosen country to act as the Reference Member State (RMS) and to be responsible for conducting and evaluating the procedure to obtain a Marketing Authorisation.²¹

2.2 Mutual Recognition Procedure (MRP)

2.2.1 Approval procedures within the EU

There are several ways to approve a medicinal product within the European Union (EU) Member States and the three EFTA Member States (Norway, Iceland and Liechtenstein). The following three procedures lead to independent national Marketing Authorisations (MAs):

National Procedure (NP)

In the National Procedure, a Marketing Authorisation is granted in one Member State (MS) according to the corresponding national law (e.g. section 21 AMG). Since January 1998, it is only possible to use this procedure to obtain a MA in one Member State. To gain the approval in more EU countries, a subsequent Mutual Recognition Procedure is necessary.²²

Mutual Recognition Procedure (MRP)

In the Mutual Recognition Procedure, a Marketing Authorisation is granted in two or more Member States. The legal provisions are laid down in Article 28(2) of Directive 2001/83/EC. The prerequisite is that one MA must have already been received in any Member State at the time of the application. This country will act as the Reference Member State (RMS) and the Marketing Authorisation will be mutually recognised in the other countries acting as Concerned Member States (CMSs). To ensure harmonisation of all Marketing Authorisations received at the end of the procedure, subsequent applications for variation must be submitted simultaneously to the RMS and the CMSs.²³

Decentralised Procedure (DCP)

In the Decentralised Procedure, a Marketing Authorisation is also granted in two or more Member States and it follows similar principles of the MRP. The legal provisions are laid down in Article 28(3) of Directive 2001/83/EC. However, at the time of the application no Marketing Authorisation of the concerned medicinal product has yet been received by the applicant in any Member State. Therefore, the CMSs are involved from the start of the procedure to grant Marketing Authorisation.²³

The following procedure leads to a single Marketing Authorisation valid throughout the EU and the EFTA Member States:

Centralised Procedure (CP)

In the Centralised Procedure, a Community authorisation that is valid for the entire EEA market (EU and EFTA) is granted. The legal provisions are laid down in Regulation EC/726/2004. The application for a Marketing Authorisation is made to the European Medicines Agency (EMA), scientifically reviewed by the Committee for Medicinal Products for Human Use (CHMP) and the final Decision is issued by the European Commission. Cases that make a CP mandatory are listed in the Annex of Regulation EC/726/2004 “Medicinal products to be authorised by the Community” and are discussed in section 2.1.2 “Special regulatory requirements for biological medicinal products” of this master thesis. According to Article 3(2) of the Regulation, the CP can optionally be chosen for a medicinal product concerned as a significant therapeutic, scientific or technical innovation or if its approval would be in the interest of public health.²⁴

2.2.2 Characteristics of the MRP

According to Directive 2001/83/EC and as described in section 2.2.1 “Approval procedures within the EU”, the Mutual Recognition Procedure (MRP) can be used to obtain a Marketing Authorisation (MA) in two or more Member States. The main difference to the Decentralised Procedure is that one MA must have already been received in a Member State at the time of the application. This Member State acts as the Reference Member State (RMS) and prepares an Assessment Report (AR) within 90 days of receipt of a valid application for a Marketing Authorisation. Before the start of the procedure, the applicant submits the application dossier to the CMSs and the RMS circulates the Assessment Report to the Concerned Member States.

Following validation by the CMS within 14 days, the Mutual Recognition Procedure starts and can successfully be closed within 90 days according to following timeline:²³

Table 1 Flow chart for the Mutual Recognition Procedure during 90 days

Day	Activity to be taken
0	RMS starts the procedure
50	CMSs send their comments concerning the Assessment Report that includes the informative texts to RMS and applicant
60	Applicant sends the response document concerning the comments of the CMSs to RMS and CMSs
68	By this Day, RMS sends the Assessment Report concerning the response document to CMSs
75	CMSs send further comments to RMS and applicant; Break-out session possible between Day 73 and 80
85	Possibility for CMSs to send remaining comments to RMS and applicant
90	CMSs notify RMS and applicant of their final position; in case of a positive consensus, RMS closes the procedure

In a subsequent national phase and within 5 days of Day 90, the applicant should send a high quality translation of the approved informative texts (Summary of Product Characteristics, Labelling and Package Leaflet) to RMS and CMSs. Within 30 days of Day 90, national Marketing Authorisations should be granted in the CMSs.²³

A “Repeat-use procedure” is possible after a first positively closed MRP. This means that a second MRP is started for the same Marketing Authorisation of the original application dossier including any variation or renewal updates. The CMSs can be new or can include a MS from which the application was withdrawn during the first MRP. It is possible to conduct several Repeat-use procedures until all Member States have been involved.²⁵

If at Day 90 no positive consensus is reached, a formal Referral to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) occurs within 7 days. This is discussed in section 5.3 “CMDh Referral” of this master thesis.

On the CMDh website, there are statistics for new applications (MRP/DCP) and Article 29 CMDh Referrals available²⁶. According to the analysis for 2009²¹, the following interpretation of the given data concerning Mutual Recognition Procedures is possible:

- 378 MRPs regarding 773 products were finalised. That is about one third of the number of finalised DCPs (1304 DCPs regarding 2788 products)
- Most of the finalised MRPs concerned an Article 10(1) generic application (255)
- 1 new active substance and 42 known active substances were approved based on an Article 8(3) full application (i.e. dossier with administrative, quality, pre-clinical and clinical data)
- Most of the finalised MRPs concerned a chemically synthesised substance (356 MRPs with chemical substances; 22 MRPs with biological substances)
- Most of the finalised MRPs concerned a prescription-only medicinal product (356)
- The third most frequently listed RMS was Germany (Denmark 18 %, Netherlands 17 %, Germany 16 %)
- 20 applications were referred to the CMDh of which agreement was reached in 12 cases. The most common grounds for Referral were due to Bioequivalence/Bioavailability (BE/BA) reasons. This can be explained by the fact that most applications concerned generic medicinal products

An advantage of the MRP over the DCP is that in the beginning, the medicinal product has already been authorised in one Member State. Therefore, the Reference Member State (RMS) has already gained experience regarding its scientific evaluation and pharmacovigilance aspects. This allows the RMS to prepare a comprehensive Assessment Report (AR) before the start of the procedure. However, in the case of a raised Potential Serious Risk to Public Health (that could not be solved), it is not possible to avoid a Referral procedure to the CMDh, including the case of a withdrawn application. In contrast, it is possible to withdraw the application in one CMS without initiating a CMDh Referral during the assessment step I of a DCP. The assessment step I of a DCP takes 120 days and leads to a closure of the procedure in case that consensus is reached. Both in an MRP and in a DCP, different brand names can be chosen in the Member States, as opposed to the Centralised Procedure, where a single brand name must be used.^{23, 24}

Further discussion concerning an MRP is provided in section 5 “Authorisation via MRP” of this master thesis.

2.3 Role of a consulting company

2.3.1 Reasons for contracting a consulting company

“Consulting” comes from the Latin word “consultare” and means “to seek advice”. A “consultant” is defined as “*a person who gives professional or expert advice*”.²⁷

In the pharma sector, a consulting company can offer its service to a wide range of companies: beginning with small biotech or medical device companies up to large multinational pharmaceutical companies acting worldwide.

Companies developing new products in the biotech and medical device sector are often Micro, Small and Medium-sized Enterprises (SMEs). Companies qualify as SMEs when they comply with the criteria laid down in the Commission Recommendation 2003/361/EC. These criteria are that the number of employed persons, the annual turnover and the annual balance sheet, respectively, fall below certain limits²⁸. Due to the small number of employees and a limited budget, these companies can benefit from the concerted assistance (for example, by providing the necessary equipment) and knowledge of a consulting company.

Furthermore, foreign companies can benefit from the local knowledge and expertise of an external service provider that is based in the country in which the main regulatory activity is planned to take place. This could be, for example, the country that acts as Reference Member State (RMS) in a Mutual Recognition or Decentralised Procedure. Moreover, the applicant can also benefit from a consulting company not located in the country of the RMS due to its experience within several large application procedures with different countries acting as RMS.

However, even large pharmaceutical companies with numerous employees worldwide can benefit from using the services of a consultancy company. The reasons could be to improve the collaboration among divisions or to profit from the best-practice experience the consulting company has gained. Service can also be required when unexpected requests by authorities or the development of a new product create sudden staff shortages.

2.3.2 Interface between pharmaceutical industry and Competent Authorities

An external service provider can act as a specialist in a variety of consulting roles. Within the context of Drug Regulatory Affairs (DRA), the following are possible areas for reasonable support by a consulting company:

- Project management and strategic planning, such as identifying global markets
- Preparation of the registration dossier or an Investigational Medicinal Product Dossier (IMPD) in the format of the Common Technical Document (CTD) / electronic Common Technical Document (eCTD)
- Preparation of the informative texts (Summary of Product Characteristics, Labelling and Package Leaflet) and conduction of a Readability User Testing (RUT)
- Obtaining approval/registration of a product (in particular in the case of complex medicinal products, such as biologicals and biosimilars) and regulatory maintenance of approved/registered products
- Market access, advertising and reimbursement
- Taking responsibilities, such as a Qualified Person for Pharmacovigilance (QPPV)

In this master thesis, the role of a consulting company in a Mutual Recognition Procedure (MRP) encompassing many countries will be discussed. If a consulting company contributes in such long-term projects, it can have the role of an interface between the pharmaceutical company and the National Competent Authorities (NCAs). This could mean that the consultancy provides the above-mentioned services and additionally takes responsibility for communicating with the authorities on behalf of the applicant in nearly all issues.

However, possible limits for an external service provider have to be considered. A lack of integration in applicant's internal structures can lead to inefficiencies and prevent a consulting company from effectively fulfilling its role. Therefore, a clear responsibility assignment must be defined clarifying the tasks for which the consulting company is engaged. Additionally, a contact person from the applicant's side should be available during the entire application procedure to resolve further questions or taking decisions in collaboration with the consulting company.

3. Case study description

The following chapters of this master thesis will give an idea of how a Mutual Recognition Procedure (MRP) with a biological medicinal product can be managed from a consulting company's point of view. Special attention will be paid to regulatory strategies and potential challenges in every relevant step, namely before, during and after authorisation of the medicinal product via MRP. Due to the complexity of biological medicinal products, these products have special requirements in each of the above-mentioned steps (see also section 2.1.2 "Special regulatory requirements for biological medicinal products"). These will be demonstrated with the help of the case study.

Key data for the case study to be discussed are as follows:

Table 2 Key data for the case study

Key data	Description
Type of procedure	Mutual Recognition Procedure
Reference Member State	Germany (Paul-Ehrlich Institute)
Concerned Member States	AT, BE, CY, CZ, DK, FI, FR, NO, PL, PT, SE, UK (12 CMSs)*
Timeline	Submission date according to CMDh-Recommendations ²⁹
Submission format	electronic Common Technical Document (eCTD)
Involved parties	Applicant (not located in RMS), consulting company (located in RMS) and National Competent Authorities
Type of medicinal product	Allergen product
Project starting point	Approval in Germany – Section 25(1) AMG
Project objective	Approval in all CMSs – Article 28(2) of Directive 2001/83/EC
Side project	Duplicate application in Germany – Sections 21ff. AMG**

* For further clarification, see Annex 1 "Map of the European Union" of present master thesis.

** There is no definition of a "duplicate" in the European pharmaceutical legislation. A duplicate is considered as an independently approved medicinal product which however refers to the same dossier and has the same legal basis as the first application (here: a nationally approved medicinal product, with the Marketing Authorisation granted in Germany within the last 5 years). Both medicinal products have different trade names and will be handled separately.^{30,31}

In a recently published Frequently Asked Questions document “National duplicates according to Section 21 AMG concerning DC/MR-Procedures” (14.04.2011)³², the BfArM recommends a new strategy for the submission of national duplicate applications. They should be submitted only after completion of the Mutual Recognition Procedure and the national phase of a Decentralised Procedure, respectively. This leads to several advantages, such as:

- No archiving of the duplicate applications during the EU procedure is required
- No time for submission and evaluation of subsequent updates is required as a compiled version of the dossier including commitments from the EU procedure will be submitted
- The handling time for the evaluation of the dossier can be accelerated in case that the applicant submits a thoroughly prepared application, especially with focus on the informative texts

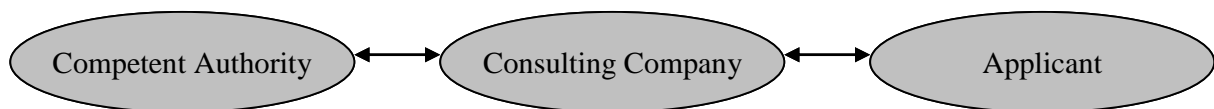
To date, this FAQ document has not been implemented in the PEI website.

4. Before Authorisation via MRP

4.1 Preparation and regulatory strategies from a consulting company’s point of view

In the beginning of such a large project as specified in section 3 “Case study description”, the tasks of each involved party must be clearly defined and recorded. If it is planned that the consulting company contributes during the whole Mutual Recognition Procedure (MRP) including the national phase, it may act as an interface between the Competent Authorities and the applicant as follows:

Figure 1 Role of a consulting company as interface



This means that there predominantly is no direct contact between the Competent Authority and the applicant. The consulting company acts as the authorised person on behalf of the applicant. Therefore, a letter of authorisation for communication on behalf of the applicant is required and must be submitted within the Module 1.2 Application form, Annex 5.4. This power of attorney must include wording such as “<applicant> herewith authorises <consulting company> to act on behalf in all matters related to the Mutual Recognition Procedure for the following medicinal products”. An example for a power of attorney is attached in Annex 2 of this master thesis. However, the applicant should ensure that the consulting company reports

on a regular basis and that he will be conferred with by the consultancy in case of complications.

In the case of the previously detailed, the responsibility assignment between applicant and consulting company could be as follows:

Table 3 Responsibility assignment between applicant and consulting company

Tasks for the consulting company	Tasks that still remain for the applicant
<ul style="list-style-type: none"> - Organisation of the whole approval procedure and the subsequent national phase - Compilation of the necessary documentation for the application dossier and its submission to the authorities - Corresponding with the authorities, especially with the RMS, in all related matters - Managing Scientific Advice meetings or Break-out sessions. 	<ul style="list-style-type: none"> - Providing the necessary information for the preparation of the application dossier and for the preparation of response documents during the procedure, if necessary - Participation in Scientific Advice or Break-out sessions - Availability for taking decisions

In addition to a clear responsibility assignment, a close contact between the consulting company and the applicant is required. Therefore, the applicant should name contact persons to the consultant that are responsible for resolving questions and taking decisions in collaboration with the consulting company, if required.

It is possible to choose a consulting company that can prepare all scientific documentation and response documents during the procedure. On the other hand, if these documents are provided by the applicant, the consulting company can take responsibility for the preparation of Module 1 with regard to contents as well as for preparing and conducting the whole procedure. In this case, it could be agreed that the Drug Regulatory Affairs Manager (DRAM) of the consulting company checks the documentation before submission, for example by ensuring that the response documents provide appropriate responses and do not miss the point.

The following questions refer to the available resources of the applicant and the consulting company and must be individually clarified:

- Who prepares the Modules 1 – 5?
- Who prepares the electronic Common Technical Document?
- Should there be further consultants or Local Operating Companies (LOCs) involved located in the other countries than the RMS? How can the communication channel clearly be defined so that there is only one contact person for the authorities?

The right choice of the Member States involved, especially of the Reference Member State, is an important strategic decision, usually decided by the marketing department of the applicant. However, the consulting company can help in the decision-making process. Before the start of the MRP, the national requirements and requested fees of each favoured Member State should be thoroughly researched. There are several sources to obtain this information, such as:

- European Commission, Notice to Applicants, Volume 2A, Chapter 7
“General information”³³
- Websites of the National Competent Authorities. However, they are not always translated into English
- Local consulting companies
- Commercial regulatory databases, such as IDRAC®

Furthermore, it is important to check whether there is already experience gained in the corresponding countries with other medicinal products intended for a similar indication or containing similar active substances. This is especially important in the context of allergen products due to a very unequal level of specific knowledge in the different countries. The CMDh publishes a tracking table that provides information about former applications referred to the CMDh in accordance with Article 29(1) of Directive 2001/83/EC. It lists the procedure number, the concerned product, reasons for Referral to CMDh and the outcome.³⁴ This detailed information allows a first evaluation on how the favoured countries act in a large procedure, such as the MRP, and what questions can be expected.

The submission date of the application to RMS and CMSs should be discussed in advance. An MRP takes about 90 days, including a possible Break-out session. National holidays should be taken into account. However, the greater the number of countries involved, the more difficult this becomes. The date of submission should be selected in line with the CMDh

document “Recommendation on Submission Dates”.²⁹ This ensures that significant dates, like Day 50, do not fall over the Christmas to New Year period of time. Furthermore it is recommended to agree the submission date with the RMS in advance.

The CMS have 14 days for formal validation of the application. Common grounds for invalidation are described on the CMDh website³⁵. According to that, a missing or incorrect fee is a frequent reason for delayed validation. There are some countries that require a fee to be paid in advance (e.g. CZ) and others that request the fee upon invoice (e.g. AT). The national requirements with regard to the Member States named in the case study will briefly be discussed below in the section 4.2 “Specifics for a biological medicinal product with regard to the case study”.

4.2 Specifics for a biological medicinal product with regard to the case study

In the case of approving a therapy allergen in an MRP with Germany as the RMS, the Paul-Ehrlich Institute (PEI) is the Competent Authority. Therefore, the consulting company requires a power of attorney for the PEI to correspond and proceed on behalf of the applicant.

The PEI will provide the assessment reports on quality, safety and efficacy based on its expertise on biological medicinal products and it will coordinate the MRP between the applicant and the Concerned Member States. As allergen products are of a complex nature, close contact to the Competent Authority at all stages of the procedure is strongly recommended. A locally based Regulatory Affairs Manager speaking the language of the RMS can solve possible problems more easily than an applicant not located in the RMS. However, as English is the official language used in all European approval procedures, a consulting company can also be engaged for a procedure with an RMS located in another Member State.

First of all, a clear task responsibility assignment between the applicant and the consulting company must be conducted. This is based on the tasks the consultant offers and on the duties and responsibilities he has been engaged in. In the case that the consulting company prepares the documentation concerning Modules 2 – 5, it must take relevant guidelines into consideration. For biological medicinal products, separate guidelines are available on the EMA website¹⁷, such as “Guideline on allergen products: Production and quality issues” (EMA/CHMP/BWP/304831/2007) or “Guideline on the clinical development of products

for specific immunotherapy for the treatment of allergic diseases” (CHMP/EWP/18504/2006). When Modules 2 – 5 are provided by the applicant, it could be a reasonable agreement that this documentation should be compiled and thoroughly checked by the consulting company before submission. Furthermore, it could also be possible for an external service provider only to focus on the preparation of Module 1. This Module contains administrative, regional or national information. If the application dossier is prepared in eCTD format in compliance with the latest eCTD specification (v3.2.2, as well as v1.3 for the regional Module), both the regional and the common parts can be handled and a regulatory life cycle management is possible.³⁶

The section “Additional Data” of Module 1 is to be used for nationally required documents³⁷. With regard to the approval of an allergen product in the Member States described in the case study, the following are examples for required documents to be included in section “Additional Data” of Module 1 (see also Annex 3 “Examples of Additional Data” of present master thesis):

Germany

A form “Annex to application for sera, vaccines, blood products and allergens” with the original signature of the manufacturer is required. The manufacturer declares that he will permit the PEI to conduct inspections. Furthermore, a rough layout of the premises and rooms has to be attached.³⁸

France

A “Form to fill in and to append to any correspondence or submission in the context of MA” is required. It provides basic information on the concerned product, company, type of procedure, type of dossier and fees.³⁹

Poland

A statement by the applicant is required that he will submit samples of the medicinal product on request of the Polish Agency.³³

Since the procedure will only be started when the correct fee has been paid, the respective Cost Regulations of the Member States should be checked immediately before submission, in

order to ensure that it is up-to-date. Some authorities require fees paid in advance of the submission including a proof of payment, other send invoices later on. In the case study, the following countries require a payment in advance and a proof of payment submitted within Module 1.2 Application form, Annex 5.1: BE, CY, CZ, FR, PL, PT and UK. The fees in AT, DE, DK, FI, NO and SE have to be paid upon receipt of an invoice.

Due to the complexity of biological medicinal products, it is recommended to seek consultation in advance of the application for Marketing Authorisation. The PEI offers Scientific Advice in several areas, such as consultation about test and therapy allergens.⁴⁰ The requirement of a Risk Management Plan (RMP) to identify and minimise risks relating to the medicinal product is one important topic to be discussed. The procedure of Scientific Advice with regard to an allergen product will be discussed in the section 4.3 “Scientific Advice” below.

According to Regulation (EC) No 1901/2006 (“Paediatric Regulation”)⁴¹, any application dossier for a new medicinal product should include the results of clinical studies conducted in line with an agreed Paediatric Investigation Plan (PIP). The PIP provides details for the development and authorisation of the medicinal product for the paediatric population, as well as a discussion on how the formulation can be adapted for children. This document must be agreed by a scientific committee of the EMA, the Paediatric Committee (PDCO) at an early stage of the medicinal product development. If the applicant requests a Waiver (e.g., when the disease occurs only in adults) or a Deferral (e.g., when it is appropriate to conduct clinical studies in adults prior to starting these studies in the paediatric population), full justification must be provided to the PDCO.⁴² The EMA Decision on an agreed PIP, a Waiver or a Deferral has to be submitted within Module 1.10 “Information relating to Paediatrics” of the application dossier.⁴³

Regarding allergen products, the PDCO published a “Standard Paediatric Investigation Plan for Allergen Products for Specific Immunotherapy” that includes a standard study design with measures that are considered necessary for the development in children.⁴⁴ The reason for the publication of a Standard PIP is the German “Therapy Allergens Ordinance” (Therapieallergene-Verordnung, TAV)⁴⁵, in force since 14.11.2008. In Germany, therapy allergens manufactured for an individual patient on the basis of an individual prescription were excluded from the requirement for Marketing Authorisation. However, the “Therapy

Allergens Ordinance” states that therapy allergens for highly prevalent allergies, such as for allergies against birch/alder/hazel pollen, now require a Marketing Authorisation. To facilitate the workflow, a Standard PIP was released.

4.3 Scientific Advice

In accordance with Directive 2001/83/EC and its transposition into national law, the Paul-Ehrlich Institute (PEI) offers scientific and procedural advice to discuss questions that the applicant has at any stage of development of a medicinal product and prior to the submission of an application dossier. This is to avoid major objections during the evaluation of the application and to increase the possibility for a positive outcome, i.e. the approval of the concerned medicinal product. Possible reasons for consulting the authority might be:

- Introducing the assessor in the whole project
- Prospective discussion of the design for Clinical Trials
- Discussion on how to generate appropriate data for obtaining a licence and whether the planned studies should be sufficient for demonstrating safety and efficacy
- Discussion of several options for presentation of the labelling

However, it must be kept in mind that the answers given by the PEI only reflect current scientific knowledge and thus, are not legally binding. Furthermore, the PEI will not pre-evaluate the data planned to be submitted. Since the PEI is an expert on biological medicinal products, it is also represented on the EMA’s Scientific Advice Working Party (SAWP) which is in charge of all European advice. The applicant may request Scientific Advice from any National Competent Authority as well as from the EMA/SAWP, regardless of whether the medicinal product falls within the mandatory scope of the Centralised Procedure or not.^{40, 46} In section 3. “Scientific Advice” of the application form, the applicant must specify whether there was Scientific Advice given by the CHMP/SAWP or by any Member State. A copy of the Scientific Advice minutes must be submitted within Module 1.2 Application form, Annex 5.14.⁴³ The applicant should therefore consider from which authority he requires advice. In our case study, i.e. for an MRP, it is advised to start nationally with a Scientific Advice request to the RMS and then possibly followed by CMSs’ authorities. However, if a biosimilar should be approved, also within an MRP, it is reasonable to first seek advice from the EMA in order to discuss the required comparability studies with the Scientific Advice Working Party/Biosimilar Medicinal Products Working Party.

A Scientific Advice request to the PEI is subject to fees and has no definite timeline. However, it should be scheduled as early as possible in order to allow adaptation of the project plan to be in line with the outcome of the consultation meeting. For the area “test and therapy allergens”, Scientific Advice is provided by experts from the division “Allergology” of the PEI. If possible, advice should be applied for three months before the desired meeting. The following documentation should be submitted in advance to the meeting:⁴⁰

- Cover letter and letter of authorisation
- Indication of the topics to be discussed together with a List of Questions (LOQ)
- Supportive briefing documentation relevant for the advice
- Agenda and a list of participants (at least two weeks before the meeting)

With regard to the case study, the following could be potential topics to be discussed with the PEI:

Procedure-related questions

- Discussion of the latest developments since granting of the national Marketing Authorisation in Germany and its impact on the planned Mutual Recognition Procedure
- Discussion of the countries to be involved
- Discussion of a potential Repeat-use procedure
- Discussion of the proposed variation sequence planned to be submitted before the start of the “first wave” or in advance of a potential “second wave” (the Repeat-use procedure following the first closed MRP)
- Coordination of the side project, an application for a national duplicate: how can the approval procedure and subsequent variations procedures be handled to be in line with the MRP?

Scientific questions

- Discussion of the latest developments since granting of the national Marketing Authorisation in Germany and its impact on the dossier/need for an update
- Modifications of the Summary of Product Characteristics (SmPC) due to new clinical data

- Need for a Risk Management Plan (RMP) and discussion of potential risks that require further evaluation

The meeting could be organised and managed by the Drug Regulatory Affairs Manager (DRAM) of the consulting company. However, due to the nature of topics to be discussed, it is advisable that further participants from the applicant side attend, including persons responsible for pharmaceutical, preclinical and clinical development. In order to familiarise the assessor to the whole project, the meeting should start with a short (electronic) presentation about the project by the DRAM. However, as the whole meeting will usually last no longer than two hours, the presentation should be kept brief. Additionally it is not intended as promotion for the applicant. Immediately after the meeting, the DRAM will draft the minutes. Questions that could not be clarified within the meeting may be discussed later in writing.

Overall, the DRAM of the consulting company should take the opportunity to establish good communication with the Competent Authority by means of being proactive and transparent. In order to modify the regulatory strategy when needed, he should ensure a close contact with the relevant assessors throughout the whole procedure and thoroughly prepare for every Scientific Advice meeting in advance.

4.4 Aspects of conducting a Readability User Testing

According to Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended, the Package Leaflet (PL) of medicinal products shall reflect the results of a Readability User Testing (RUT) in order to ensure that the PL is legible, clear and easy to use.

European guidance is provided in the “Guideline on the readability of the Labelling and Package Leaflet of medicinal products for human use”. This guideline suggests a way to test the readability of a full-colour mock-up of the PL with a group of selected test participants answering a questionnaire.⁴⁷

In the case of conducting a Readability User Testing with a PL of an allergen product, the consulting company must consider the following:

Preliminary considerations

If the allergen product is available in two strengths, for example to allow a dose escalation for an allergen-desensitising treatment, there are usually two separate Package Leaflets available. Therefore, the PL with the most extensive content should be declared as “parent PL”. The parent PL is the one that will be tested. This is usually the PL for the beginning of treatment. Since the PL for the continuation of treatment differs only in minor passages referring to product name, dosage, instructions for taking the medicinal product and contents of the pack, the test result also applies for the “daughter PL”.

Preparation of a patient-friendly Package Leaflet

A Package Leaflet for a medicinal product in the context of allergic diseases often contains information that is difficult for a layman to understand, such as the description of side effects, dose escalation or possible occurrence of an anaphylactic reaction. Furthermore, the structure of a PL must be in line with the Quality Review of Documents (QRD) templates.⁴⁸ However, there is still potential for improvement of the readability with the help of:

- Patient-friendly language, using lay terms (e.g., as proposed in the glossary published by the MHRA⁴⁹)
- Formatting: Structure of the text, letter-type, font size, colour, headings, bullet points, pointing out of important information by using bold type or spaces

Recruiting participants

In the majority of cases, the people who will use a Package Leaflet are patients. Additionally carers, such as parents, partners and friends may be involved. Therefore a range of different types of people must be recruited in order to represent the users. For that purpose, the participants may be recruited within self-help groups, parent groups or community centres, for example.⁴⁷ A Package Leaflet for an allergen product that is intended to be used in adults and children is relevant for a wide range of people. Therefore, the participants should cover a demographic group including different ages, professions, social classes and levels of education. The focus should be on the lower educated, as it is important to include people who do not use written documents in their working life and people for whom written information is difficult to understand.

Questionnaire

Before the testing period, the author of the Package Leaflet should help to design the questionnaire. Everything monitored later on during the testing period will give information on how to improve the structure of the Package Leaflet. The questionnaire should be structured in a way to show that the user is able to find the relevant information, interpret it and describe the resultant action he would take. Prior to the development of the questionnaire, key safety messages should be identified based on its importance for the treatment or in case of potential misuse. This is to ensure safety, efficacy of and compliance with the medicinal product. Questions based on the key safety messages should be included. This concerns section 4. "Possible side effects" of the PL. This is important as the patient must know that for certain side effects (e.g. anaphylactic reactions), a doctor must be informed and the treatment must be stopped immediately. The questions should appear in a random order rather than following the order of the text of the leaflet. Questions should also be phrased differently from the text of the leaflet. This avoids answers based merely on identifying groups of words. Furthermore, once participants have found the required information, they should answer in their own words, as opposed to simply reading from the located site of the patient leaflet. The questions therefore must be open-ended.

Test phases

The test is divided into three phases. In the first, the pilot phase, the PIL is tested on about three persons for a first check and to demonstrate feasibility of the test. In the second and third phases, the PL is tested with ten participants each case. Between the two phases, potential improvements in readability and comprehensibility are discussed and implemented in order to obtain satisfactory data.⁴⁷

Final report

The results of this consultation with target patient groups must be submitted within Module 1.3.4 of the application dossier and should include:⁴⁷

- Product description
- Method used, explanation on the choice of population consulted, languages tested
- Questionnaire
- Original and revised Package Leaflets

- Summary and discussion of results (subjects' answers, problems identified and revisions made to relevant Package Leaflet sections)
- Conclusion

In this case study, the medicinal product was already approved in Germany. Therefore, a Readability User Testing report had already been submitted with the national application for a Marketing Authorisation in Germany. If this old test report will be submitted with the application for Marketing Authorisation via MRP, an introductory statement is usually necessary. This statement should include a comparison between the PL tested and the current approved PL to show the differences, for example due to variations submitted in the meantime. The statement should also declare whether the changes are minor and whether the PL can be considered as equally readable and comprehensible. However, if major changes have been introduced in the Package Leaflet following the first approval, a new Readability User Testing is necessary with the current PL. The results of a Readability User Testing must be presented in English for the Mutual Recognition Procedure⁴⁷. In the application dossier for a national duplicate that is submitted after completion of the MR-Procedure, it is possible to refer to this Readability User Testing.³²

5. Authorisation via MRP

5.1 Process and potential challenges from a consulting company's point of view

The Mutual Recognition Procedure (MRP) is used to obtain a Marketing Authorisation in several Member States on condition that the medicinal product has already received Marketing Authorisation in any Member State at the time of application (see also section 2.2.2 "Characteristics of the MRP"). From the point of view of a consulting company acting on behalf of the applicant, the following key steps of the procedure require action from the consulting company:²³

Before Day 0 of MRP

- Informing the RMS about the planned MRP and agreement on a timetable
- Request for Scientific Advice meetings, thorough preparation and managing of the meetings
- Consolidation of the Marketing Authorisation dossier to ensure that it reflects all changes made by variations since obtaining the MA and, if necessary, update of the

- dossier by means of variations in order to comply with technical and scientific progress and to ensure adequate manufacturing and control of the medicinal product
- Submission of application to the RMS including a request for preparation of an Assessment Report to the CMSs and to allocate a procedure number for MRP
 - Submission of the identical application dossier to all CMSs

During MRP

- Preparation and submission of response documents to the comments raised by the CMSs

During the subsequent national Marketing Authorisation Step

- Submission of high quality national translations of the approved harmonised informative texts (Summary of Product Characteristics, Labelling and Package Leaflet) to the RMS and CMSs and further discussion to obtain acceptance of these texts

In order to be competitive, the pharmaceutical company will seek to obtain Marketing Authorisations for the medicinal product in all proposed indications and selected Member States as soon as possible. The consulting company must meet the challenge of organising a well-structured MRP with a positive outcome. Therefore, the good communication established during the Scientific Advice meetings between the Drug Regulatory Affairs Manager of the consulting company and the responsible assessor in the RMS should be maintained during the whole procedure.

When scientific questions cannot be clarified or fundamental disagreement occurs on the way to obtain the Marketing Authorisation, the consulting company is challenged to clarify within the following procedural steps:²³

Break-out session

A Break-out session can be organised between Days 73 to 80 of the MRP in order to resolve outstanding issues and to avoid a Referral to the CMDh. European guidance is provided in the “Best Practice Guide on Break-out sessions for Mutual Recognition and Decentralised Procedures”⁵⁰. CMSs should notify the RMS and the applicant by Day 50 at the latest about a

possible concern of a Potential Serious Risk to Public Health (PSRPH) that unsolved would lead to a Referral procedure according Article 29(3) of Directive 2001/83/EC. The consulting company should take the opportunity to participate in the meeting and to ensure a well-structured and effective dialogue. It is reasonable that representatives from the applicant side also attend in the meeting in order to allow decision making.

CMDh Referral procedure

If the concern for a Potential Serious Risk to Public Health was raised by any of the Member States involved in the procedure and could not be clarified during a Break-out session, the matter will be referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - human (CMDh). This procedure will take 60 days and is described in section 5.3 “CMDh Referral” of this master thesis. The consulting company, together with representatives from the applicant side, should take the opportunity to explain their point of view in a written procedure or in an oral hearing.

CHMP Arbitration procedure

If the CMDh Referral procedure failed and no agreement was reached, the matter will be referred to the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA). This committee must be informed about the reasons for disagreement and will take responsibility within an Arbitration procedure leading to a final Decision by the European Commission (EC). This Decision remains binding for future Repeat-use procedures with other Concerned Member States. However, if different grounds for a PSRPH result from such a Repeat-use procedure, they must be discussed again during CMDh Referral and CHMP Arbitration procedure.

5.2 Specifics for a biological medicinal product with regard to the case study

The process of a Mutual Recognition Procedure with 12 Concerned Member States and Germany as Reference Member State must be well prepared, as described in section 4.1 “Preparation and regulatory strategies from a consulting company’s point of view”. National requirements, such as the languages to be used for the dossier (e.g. Portugal requires the EU application form in Portuguese), the number of copies and the need for samples (e.g. Poland requires a written statement that samples will be provided upon request) must be evaluated for each Member State. European guidance is provided in Notice to Applicants, Volume 2A,

Chapter 7 “General Information”. However, it is necessary to check the validity of this information on the respective websites of the National Competent Authorities.

The Paul-Ehrlich Institute prefers the use of the electronic Common Technical Document (eCTD) format for submissions in order to guarantee lifecycle management⁵¹. EU guidance is provided by the Telematics Implementation Group – electronic submission (TIGes) “Guidance for Industry on Providing Regulatory Information in Electronic Format: eCTD electronic Submissions”³⁷ and by the CMDh “Best Practice Guide on the use of the electronic Common Technical Document (eCTD) in the Mutual Recognition and Decentralised Procedures”⁵². However, it is yet to be determined whether additional paper copies are required for each of the Member States.

In the case of an allergen product that exists in two strengths, the submission concerns two applications with two different procedure numbers. In Notice to Applicants, Volume 2A, Chapter 2 “Mutual Recognition”, the generation of this number is described. According to this document, the procedure numbers are as follows: DE/H/nnnn/001/MR and DE/H/nnnn/002/MR (nnnn is a specific number for the medicinal product and is allocated by the RMS). Both strengths of one product can be combined within one eCTD structure.⁵¹

On the CMDh website, a draft cover letter for the submission of new applications in the MRP is published. According to this letter, the following information must be included in addition to the procedure related details:⁵³

- A statement that the submission dossier is provided electronically in eCTD-format
- Confirmation that the History of Sequences (Tracking Table) is attached. An example of a Tracking Table prepared in line with the before-mentioned CMDh Best Practice Guide and the case study is provided in Annex 4 of this master thesis
- Confirmation that the submission is checked with an up-to-date and state-of-the-art virus checker
- Information about the submission of duplicate applications
- Confirmation that the relevant fees have been paid, if applicable
- Confirmation that the dossiers submitted to RMS and CMSs are identical
- Confirmation that the content of the electronic submission is identical to the paper version, if applicable

For the submission, it is mandatory to use the application form provided on the website of the European Commission, Notice to Applicants Volume 2B, “Application form”.⁴³ With regard to the case study, the following must be considered:

- For each strength of the allergen product, a separate application form is required
- The application form has to be signed by the person authorised for communication on behalf of the applicant
- Under section 4.2 “Marketing Authorisation for the same product in the EEA”, the national authorised product in the RMS has to be given and the nationally approved duplicate medicinal product, if applicable

On the CMDh website, contact e-mail addresses are listed for the submission of several documents, such as the submission of electronic response documents in the MRP.⁵⁴ During the whole procedure, close contact between the consulting company acting on behalf of the applicant and the Paul-Ehrlich Institute acting as the Competent Authority should be maintained. Therefore, it is recommended to send a draft response document to the RMS before it will be officially submitted to the RMS and CMSs via the above-mentioned addresses.

5.3 CMDh Referral

The Coordination Group for Mutual Recognition and Decentralised Procedures - human (CMDh) was set up according to Article 27(1) of Directive 2001/83/EC, as amended, and had its initial meeting on 14 November 2005. The tasks of the CMDh are based on its mandate that was endorsed by the Heads of Medicines Agencies (HMA).⁵⁵ The CMDh meets once a month in line with the CMDh calendar published on the HMA website and one of its tasks is to try to solve any problem related to the Mutual Recognition or Decentralised Procedure at an European level.^{55,56} The CMDh offers advice based on a defined procedure. However, the content of advice does not include scientific questions in the context of developing a medicinal product. This is the task of the National Competent Authorities or the CHMP/Scientific Advice Working Party (see also section 4.3 “Scientific Advice”). Furthermore, any procedural questions should first be discussed with the RMS. If the question cannot be answered, the CMDh member of the respective state will bring the question for discussion to the CMDh. The discussion will usually take place within 30 days after the question has been received by the CMDh secretariat.⁵⁷

In order to make the information available to all interested parties, the CMDh continually develops guidelines, recommendations and Standard Operating Procedures (SOPs) that can be found on the website of the HMA.⁵⁸

As already mentioned in this master thesis, a main task for the CMDh is to reach agreement between the Member States when a Potential Serious Risk to Public Health (PSRPH) is identified by any of the Member States during the application procedure. This PSRPH can be based on the assessment report that the RMS has circulated or on the therein included informative texts (Summary of Product Characteristics, Labelling and Package Leaflet). According to Article 29(3) of Directive 2001/83/EC, the application concerned will be referred to the CMDh. Applications that apply to such a procedure are: Mutual Recognition Procedure, Decentralised Procedure and follow-on procedures, such as variations or renewal procedures.⁵⁵

Examples for the definition of a PSRPH are given in the “Guideline on the definition of a Potential Serious Risk to Public Health in the context of Article 29(1) and (2) of Directive 2001/83/EC”. According to this guideline, a PSRPH is defined as a “*situation where there is a significant probability that a serious hazard resulting from a human medicinal product in the context of its proposed use will affect public health*”. However, the definition must always be interpreted in relation to the overall risk-benefit analysis.⁵⁹ A PSRPH in the case of biological medicinal products could be the fact that a biological medicinal product failed to show biosimilarity within a comparability exercise to its reference product and therefore cannot guarantee to have the proposed therapeutic efficacy.

The Concerned Member State that found a PSRPH must notify the CMDh secretariat at Day 90 of a Mutual Recognition Procedure. The secretariat, located at the EMA, then proposes a date for the start of the Referral procedure, usually no later than 30 days after Day 90. Since in this procedure, all CMDh members are invited to be involved, the RMS has to provide the necessary basic information (Assessment Report, informative texts and reasons for the Referral) to all other Member States not concerned with the Mutual Recognition.⁶⁰

The Article 29(3) Referral procedure is led by the RMS and can successfully be closed within 60 days. Within this 60 days period, the applicant prepares a response document by Day 25 to

answer the Day 10 List of Questions (LOQ). Additionally, the applicant has the possibility for scientific discussion within an oral explanation meeting around Day 50. Guidance on oral explanations is provided in the Annex of the CMDh SOP “Disagreement in Procedures – Referral to CMDh”⁶⁰. For the applicant, or its authorised representative, an oral explanation can be a chance to present its point of view at the CMDh meeting. In order to allow scientific discussion, not more than five persons from the applicant side should participate in this meeting and participants must be well prepared. The list of attendees along with an explanation of its functions within the meeting and the presentation must be submitted to the RMS, the CMDh members and the secretariat in advance in electronic format. The meeting should optimally be executed as follows:

Time for the CMDh members to give a résumé before arrival of the applicant

The RMS summarises the reviewed response document, any comments on new proposed texts and the remaining issues of concern.

Time for the applicant to explain its point of view

The applicant orally explains its point of view, preferably with the aid of a computer-assisted presentation, for no longer than 20 minutes. Focus is on the most relevant questions, required changes in the informative texts and an outlook of potential commitments to be made.

Time for the CMDh members and the applicant to get into discussion

In a question and answer session during the next 20 minutes, outstanding issues should be clarified.

Time for the CMDh members for subsequent discussion when the applicant has left the room

The discussion is continued and a final agreement on the outcome of the procedure should be reached.

If no agreement could be reached within the oral explanation meeting, the remaining days until Day 60 are used to obtain an agreement. In the case of final disagreement, the unresolved issues will immediately be referred to the European Medicines Agency for Arbitration within the CHMP.

5.4 National Marketing Authorisation Step

Within a 90 days Mutual Recognition Procedure with a positive outcome, that is maybe prolonged by a CMDh Referral and a CHMP Arbitration procedure, all Concerned Member States have agreed to the Assessment Report of the RMS and the informative texts in English. Subsequent to this procedure, the national Marketing Authorisation step follows. This step is necessary to grant single national Marketing Authorisations in each of the Concerned Member States. According to Notice to Applicants, Volume 2A, Chapter 2 “Mutual Recognition”, this national phase should take 30 days. Therefore, the applicant is requested to submit high quality national translations of the approved harmonised informative texts (Summary of Product Characteristics, Labelling and Package Leaflet) to RMS and CMSs within 5 days after the end of the procedure. The translated texts should be sent to the addresses published in the CMDh document “Contact addresses for submission of translations in MRP and DCP”.⁶¹

However, in practice the national Marketing Authorisation step can take much longer than 30 days. In order to receive the national Marketing Authorisations as soon as possible, a very good preparation of this phase in general and of the translated texts is necessary. The national requirements for submission of the texts (e.g. naming of the files, structure and formatting of these documents) must be thoroughly evaluated by studying the relevant websites of the National Competent Authorities. Otherwise, extensive discussions between a National Competent Authority and applicant may be required. During such a discussion an exchange about the texts would be necessary, which would require several eCTD sequences. In order to simplify this step of the procedure, the CMDh and HMA have agreed that the discussion of national translations can be handled outside the eCTD.⁵²

The national texts must comply with the QRD product information templates published on the EMA website.⁶² In addition, the so-called blue box requirements must be considered. They are listed in Notice to Applicants, Volume 2A, Chapter 7 “General Information” and concern additional information nationally required on the Labelling and the Package Leaflet, respectively. Examples of blue box requirements for the countries listed in the case study are:

- AT (Package Leaflet): MA-No.: should be indicated as “Z.Nr.”
- BE (Package Leaflet): The telephone number of the poison centre should be mentioned

- DK (Labelling): Products which may reduce the ability to drive or use machines must have a warning triangle
- FI (Labelling): A special Nordic number “Vnr” must be stated

If a combined multi-lingual labelling for the Nordic countries Denmark, Norway and Sweden is planned, the process is more complex, because three Competent Authorities are involved. This requires extensive discussion on the respective mock-ups.

For a consulting company coordinating the national Marketing Authorisation step, further challenges must be managed as follows: it must be clarified who should prepare the national texts. If a translation bureau is engaged, it is still necessary to check the translated texts with regard to regulatory requirements. These include the QRD-templates, blue-box requirements, standard terms, excipients guideline and “Terms for Substances” (“Stoffbezeichnungen” in Germany). Furthermore, the responsible person for the submission of the texts should be determined. Authorities usually prefer one contact person. If consulting companies located in the other Member States are involved, letters of authorisation are required.

Contrary to medicinal products authorised in the Centralised Procedure, in an MRP each Competent Authority can approve a different name for the medicinal product. However, if the medicinal product is packed in a blister and the pharmaceutical company intends to produce one common blister for all countries, having only one name is more practical. In this case, the choice of the name should be discussed with the National Competent Authorities during the procedure. Due to linguistic and historical differences, not all Member States may accept the same name. A change of the name of the medicinal product may be undertaken as part of the national Marketing Authorisation step when the Competent Authority has agreed to it, in order not to make a subsequent Type IB notification procedure (after approval) necessary.^{14, 63}

Finally, if the national Marketing Authorisations are obtained, a press release could include information about:

- Presentation of the advantages related to the medicinal product
- The date of Marketing Authorisation and the concerned countries
- The proposed date for launch of the product on the market
- The next planned steps in Europe, such as further countries planned to be involved

6. After Authorisation via MRP

6.1 Maintaining the Authorisation from a consulting company's point of view

When the Marketing Authorisation Holder (MAH) has obtained Marketing Authorisation for the medicinal product, he can start to place the product on the market (after price negotiations that are necessary in some countries). However, from the time of approval, several regulatory activities are required in order to maintain the Marketing Authorisation and to comply with scientific progress and legal revisions.

It must be individually agreed and stipulated by contract which tasks of the regulatory lifecycle management should be taken by the consulting company. If the consulting company acts on behalf of the MAH, a letter of authorisation will be required for correspondence and proceeding with each National Competent Authority. As single national Marketing Authorisations are obtained with a Mutual Recognition Procedure (MRP), the consulting company should also have expertise on the national law for human medicinal products valid in that respective country. The consulting company should have a network with other external service providers located in the other Member States in place. The following are general tasks to maintain the Marketing Authorisation and to ensure a correct lifecycle of the approved medicinal product:

“Sunset Clause”

In accordance with Article 23a of Directive 2001/83/EC, the Marketing Authorisation Holder (MAH) must inform its National Competent Authority about the date of actual placing of the medicinal product on the market and of each cessation of marketing. “Placing on the market” in this context means the release into the distribution chain. This information is necessary to fulfil the requirements of the so-called “Sunset Clause” laid down in Article 24(4) of Directive 2001/83/EC. According to this Directive, the Marketing Authorisation ceases to be valid in the following cases:

- The medicinal product is not placed on the market within three years of the approval
- The medicinal product is not marketed for a period of three consecutive years

To maintain valid Marketing Authorisation, it is sufficient to market at least one presentation and at least one of the approved pack sizes. Exemptions may be granted due to exceptional circumstances and on public health grounds.²²

Renewal

A Marketing Authorisation (MA) obtained within a Mutual Recognition Procedure must be renewed after five years according to Article 24 of Directive 2001/83/EC. Therefore, a consolidated version of the dossier with regard to quality, safety and efficacy including all variations must be submitted to the Competent Authority at least six months before expiry of the MA. This allows a re-evaluation of the risk-benefit balance. The renewal procedure follows a 90 days timetable similar to a Type II variation procedure and is described in the “CMDh Best Practice Guide on the processing of renewals in the Mutual Recognition and Decentralised Procedures”. After renewal, the Marketing Authorisation is valid for an unlimited period. If the Competent Authority has justified concerns related to pharmacovigilance, an additional five-year renewal period can be arranged.⁶⁴

Variations

Changes in the Marketing Authorisation dossier may become necessary to be in line with the state-of-the-art in science, technology and current knowledge. The Competent Authority must be notified of changes in accordance with Regulation EC/1234/2008 of 24 November 2008. This Variation Regulation became effective on 01 January 2010 and replaces Regulation EC/1084/2003, which was formerly valid for Marketing Authorisations obtained in a Mutual Recognition Procedure. It provides the basis for the classification in minor changes (Type IA and Type IB notifications) and major changes (Type II variations) and to allow Grouped applications and Worksharing applications. European guidance for the respective procedures is given in the CMDh “Best Practice Guide for the submission and processing of variations in the Mutual Recognition Procedure”.⁶⁵ Handling variations is further discussed in section 6.4 “Variations and Follow-up Measures” of this master thesis.

Periodic Safety Update Reports (PSURs)

A Periodic Safety Update Report (PSUR) contains worldwide safety experience together with a critical risk-benefit analysis about the medicinal product. It is usually submitted to the Competent Authorities at defined time points (and always immediately upon request):⁶⁶

- After authorisation: every six months
- In the first two years after initial placing on the market: every six months
- In the third and fourth year after initial placing on the market: once a year
- Thereafter: all three years

In certain circumstances the frequency of PSURs can be increased, e.g. due to safety concerns, or decreased, e.g. for generic medicinal products unless potential safety concern.

6.2 Specifics for a biological medicinal product with regard to the case study

After the medicinal product is authorised via a Mutual Recognition Procedure, single national Marketing Authorisations are obtained in the Member States. Therefore, the national law in each country must be taken into account in addition to the EU legislation. The relevant contact points of the Authorities and possible deadlines for each notification procedure must be considered.

A specific requirement for biological medicinal products in the post authorisation phase is the need for batch release. In Germany, biological medicinal products such as allergens, vaccines and blood products that are manufactured in batches are subject to official batch release in compliance with section 32 AMG. The definition of a batch is given in section 4 para 16 AMG: *“A batch is the quantity of a medicinal product produced from the same amount of starting material in a standard manufacturing process or, in the case of a continuous manufacturing process, within a specific period of time.”*⁹ The PEI checks every manufactured batch to determine whether it corresponds to the approved criteria regarding quality, safety and efficacy laid down in the Marketing Authorisation dossier. In addition, the PEI sends a letter to the Marketing Authorisation Holder to inform him of the release of each batch.⁶⁷ Further details on batch release and about official medicinal product control laboratories in other Member States of the European Union is provided in section 6.3 “Batch release” of this master thesis.

An example for a procedure that is handled different in the Member States (such as electronic submission or not) is the notification procedure on the “Sunset Clause”. It must comply with the national legislation as a result of the transposition of Directive 2001/83/EC into national law. In Germany, this notification procedure must be in line with the section 29 para 1b and 1c AMG. The National Competent Authorities BfArM and BVL have developed an online procedure for above-mentioned reporting that is strongly recommended to be used. The PEI requires only a conventional notification in writing, taking the following deadlines into account:⁶⁸

- Date of placement on the market: immediate notification
- Temporary or permanent cessation of the marketing: at least two months before

In order to facilitate the procedures in which several Member States are involved, it is recommended to synchronise the dates where action of the Marketing Authorisation Holder is required. Therefore, a proposed Common Renewal Date (CRD) should be stated in the application form and subsequently be agreed between the Reference Member State and the Marketing Authorisation Holder⁴³. In case of a Repeat-use procedure, the renewal timetable should be in line with the initial renewal timetable. Furthermore, a harmonisation of the PSUR submission cycles is desirable.⁶⁴

From a strategic point of view, it must be considered that most of the procedures in the post approval phase are relevant for all Marketing Authorisations obtained within the Mutual Recognition Procedure. That is to say, the submission of, for example, variation applications, renewal applications and activities with regard to pharmacovigilance, such as Urgent Safety Restrictions (USRs), are necessary for all Member States. This requires time (prior discussion with National Competent Authorities, evaluation of the national requirements) and money (most of the countries charge fees for each procedure). Furthermore, even if the product is not marketed, it is necessary to maintain its Marketing Authorisation dossier. Therefore, the Marketing Authorisation Holder has the possibility for a final withdrawal of one or more of its Marketing Authorisations obtained within a Mutual Recognition Procedure. A request for withdrawal must be submitted to the Competent Authority in line with the national requirements (e.g. use of special forms for withdrawal available on the national websites of the authorities) and the Reference Member State (RMS) must be informed. In case of a withdrawal of the Marketing Authorisation in the current RMS, a new RMS has to be

appointed. Advice to the MAH is given in the CMDh “Position on changing the Reference Member State”.⁶⁹

6.3 Batch release

As mentioned above, all biological medicinal products such as allergen products that are manufactured in batches in Germany require official batch control and batch release by the Competent Authority. The legal basis in Germany is section 32 AMG “Official batch testing”. Here it is stated that the aim of an official batch testing is to show that the batch has been manufactured and tested by methods that comply with the current standard of scientific knowledge and that the required quality, safety and efficacy conform to those defined in the Marketing Authorisation. Therefore, the PEI must release every manufactured batch in Germany. The Marketing Authorisation Holder may not place the batch on the market without having received an official release note from the PEI.⁷⁰ However, an exemption from that obligation is laid down in section 32 para 4 AMG: the official batch release is not mandatory in case that the manufacturer has established manufacturing and control methods that guarantee the quality, safety and efficacy of the respective batch.

The definition of allergen products laid down in the AMG (see section 2.1.1 “Definition of a biological medicinal product”), differs between therapy allergens and test allergens. With regard to experimental batch testing, the following applies:⁷⁰

- Therapy allergens: test are conducted on the intermediate or on the finished medicinal product
- Test allergens: test are solely conducted on the finished medicinal product

The Paul-Ehrlich Institute is the only authority in the European Union for official batch release testing of therapy allergens and test allergens. The Paul-Ehrlich Institute releases about 2000 batches every year related to allergen products. For official batch release activities, the PEI makes out an invoice based on the fees laid down in the “Statutory Cost Regulation for official duties of the Paul-Ehrlich Institute pursuant to the Medicinal Products Act” (Kostenverordnung für Amtshandlungen des Paul-Ehrlich-Instituts nach dem Arzneimittelgesetz).⁷⁰

The specification for official batch testing including all test parameters is described in the Monograph “Allergen Products” of the European Pharmacopoeia (Ph. Eur.). The Ph. Eur.

states that the test of the finished product must include immunological controls (such as the overall immunological activity), chemical controls (such pH value and the capping) and bacteriological control (such as sterility). The last update of this Monograph was in the 6th edition 2010 (6.6)⁷¹ which introduced several changes increasing the quality requirements for allergen products. According to this updated Monograph, the following tests are required, unless otherwise approved:⁷²

- Verification of the presence of relevant allergen components in the protein profile, including a justification of the choice of relevant components to be tested for
- Protein content must be within 80 – 120 % of the stated content. If the biological potency can be determined, the protein content must be within 50 – 150 % of the stated content
- Activity range must be within 50 – 150 % of the stated amount. The assay is performed by inhibition of the binding capacity of specific immunoglobulin E antibodies or a suitable equivalent *in-vitro* method
- Individual allergens must be within 50 – 200 % of the stated amount of each relevant allergen component

Section 6.4 “Variations and Follow-up Measures” explains how to comply with updates of the Monographs contained in the Ph. Eur.

The necessary documents for batch release applications must be submitted to the address stated on the website of the PEI. These include:⁶⁷

- Documentation regarding the manufacture of the batch
- Record of the results for all conducted quality control tests
- Test samples of the manufactured batch to allow experimental testing

In the field of batch release, the option to submit the application electronically is not yet available, but already in the pipeline.⁷³

In addition, for immunoglobulins, vaccines and products manufactured from blood plasma, the experimental batch testing can also be conducted by an official medicinal product control laboratory in another Member State of the EU/EEA that belongs to the Official Medicine Control Laboratories (OMCL) network.⁷⁴ Since 1995, the European Directorate for Quality of Medicines (EDQM) acts as its secretariat and coordinates this network for experimental batch

testing of the above-mentioned medicinal products.⁷⁵ The testing is carried out in compliance with product specific guidelines, the Official Control Authority Batch Release (OCABR) guidelines. They include information about the required experimental tests and information for the applicant about the documentation to be supplied within the application for batch release. As a result, the corresponding Competent Authority issues an Official Control Authority Batch Release (OCABR) Certificate that is mutually recognised by all other Member States. The legal basis is provided in Article 114 of Directive 2001/83/EC. A copy of this certificate has to be submitted to the Competent Authority in that Member State where the batch will be placed on the market.⁷⁶

6.4 Variations and Follow-up Measures

The definition of a variation is laid down in Article 2(1) of Regulation EC/1234/2008. According to this Regulation, the Competent Authorities must be notified of any amendment to the documentation contained in the approved Marketing Authorisation dossier, such as a change of the content or addition/deletion of documents.⁷⁷ Amendments to details that are not part of the documentation do not trigger a variation procedure. Therefore, the documentation should be written only as detailed as necessary for the assessment. For example unnecessary equipment details with regard to pharmaceutical quality should be excluded. To avoid a variation procedure in case of changes, Standard Operating Procedures (SOPs) should neither be included in the documentation nor referred to.

Possible reasons requiring amendments of the Marketing Authorisation dossier are:

- Adjustment to the state-of-the-art in science, technology and current knowledge
- Experience with the medicinal product resulting from its application to patients in greater quantities
- Changes initiated by the Competent Authority due to new information having a bearing on the safe use of the medicinal product
- Adjustment to requirements of the market, such as for a new pack size
- Administrative changes, such as a change in the address of the MAH

Variations to Marketing Authorisations obtained in a Mutual Recognition Procedure must be submitted according to Regulation EC/1234/2008 to RMS and CMSs simultaneously. Only a few changes, such as the transfer of the Marketing Authorisation are handled as a national variation according to national law. The Regulation EC/1234/2008, also called the “new

Variation Regulation”, is effective since 01 January 2010 and replaces former Regulations EC/1084/2003 (applicable for medicinal products authorised via MRP or DCP) and EC/1085/2003 (applicable for medicinal products authorised via Centralised Procedure). The applicability for all purely national authorised medicinal products is currently in a transition period. The new Variation Regulation includes both human and veterinary medicinal products. It was prepared in order to harmonise and simplify existing legislation framework whilst maintaining equivalent levels of health protection.⁶⁵

According to Article 4 of the new Variation Regulation, the following guidelines are drawn up by the European Commission:

Classification of changes (including conditions to be fulfilled and documentation to be supplied)

“Guideline on the details of the various categories of variations to the terms of Marketing Authorisations for medicinal products for human use and veterinary medicinal products (2010/C 17/01)”, the so-called “Classification Guideline”¹⁴

Description of the variation procedures (including timelines)

“Guideline on the operation of the procedures laid down in Chapters II, III and IV of Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of Marketing Authorisations for medicinal products for human use and veterinary medicinal products (2009/C 323/04)”⁷⁸

With the aid of above-mentioned guidelines together with the CMDh “Best Practice Guide for the submission and processing of variations in the Mutual Recognition Procedure”, the applicant may classify the required changes according to their impact on quality, safety and efficacy in Type IA/Type IB notifications (minimal impact) and Type II variations (significant impact). Furthermore, he can evaluate the necessary documentation to be submitted. Changes that are not listed within the Classification Guideline are Type IB notifications by default.⁶⁵

The Classification Guideline subdivides the changes into administrative, quality, safety/efficacy/pharmacovigilance changes and changes related to a Plasma Master File (PMF)/Vaccine Antigen Master File (VAMF). Due to the complexity of biological medicinal

products (as detailed in section 2.1.2 “Special regulatory requirements for biological medicinal products”), the changes relating to biological medicinal products require extensive evaluation and special documentation to be submitted. Therefore, they are in many cases classified as a Type II variation. Type II variations follow a 60 days timetable and are subject to approval. The listed changes differ between biological medicinal products and chemically synthesised medicinal products by stating, for example, “excluding biological or immunological substances” in the heading. If the description of the change gives no information as to whether a biological medicinal product is concerned or not, the list with “conditions to be fulfilled” additionally assures that no complex evaluation is required by preconditions like “The product concerned is not a biological/immunological product”.¹⁴

The batch of an allergen product is tested in line with the Monograph “Allergen Products” on the European Pharmacopoeia (see also section 6.3 “Batch release”). In the case of a change of this Monograph, a Type IA notification is necessary to comply with this change. According to the Classification Guideline and with regard to the case study, category number B.III.2 b) applies as follows:¹⁴

Table 4 Variation details to comply with an update of the Ph. Eur. Monograph “Allergen Products”

Key data	Details
Category number	B.III.2 b)
Description	Change to comply with an update of the relevant Monograph of the Ph. Eur.
Procedure Type	Type IA
Conditions to be fulfilled	<ul style="list-style-type: none"> - The change is made exclusively to comply with the Pharmacopoeia - Additional specifications to the Pharmacopoeia for product specific properties are unchanged (e.g. particle size profiles, polymorphic form or e.g. bioassays, aggregates) - Additional validation of a new or changed Pharmacopoeial method is not required
Documentation to be submitted	<ul style="list-style-type: none"> - Amendment of the relevant sections of the dossier (presented in the EU-CTD format) - Comparative table of current and proposed specifications - Batch analysis data on two production batches of the relevant substance for all tests in the new specification - Data to demonstrate the suitability of the Monograph to control the substance, e.g. a comparison of the potential impurities with the transparency note of the Monograph

With the new Variation Regulation, “Do and Tell” for Type IA notifications and the possibility for grouping of variations is introduced. Type IA variation can be implemented prior to notification to the Competent Authorities (“Do and Tell”). These notifications should be submitted within 12 months following implementation. They should also be grouped with other Type IA variations (“Annual Report”).⁶⁵ Therefore, it is required for the consulting company, coordinating the variations procedure, to maintain a database containing the implementation dates and proposed submission dates of changes.

Furthermore, it is important to effectively coordinate the variations procedure with the Competent Authorities. Therefore, the discussion of an individual variations plan with the Reference Member State in advance of the submissions is appropriate. This variations plan could include the following details: procedure type of variation, category number according to the Classification Guideline, description of the proposed change, planned date of the submission and information about intended Grouping/Worksharing procedure, if applicable.

Moreover, the lifecycle of the purely nationally approved duplicate medicinal product (see section 3 “Case study description”) and the MRP-medicinal product has to be coordinated. In Germany, the new Variation Regulation has not yet been implemented for medicinal products authorised by purely National Procedures⁷⁹. Therefore, there is a different legal basis for changes (Section 29 AMG) and different timelines (e.g. changes subject to approval take 3 months in Germany) regarding the nationally approved duplicate from the medicinal product that is based on an MRP. Following discussion of the variations plan with the RMS, it is reasonable to submit the MRP-variations first. In case of Type IB or Type II variations, the Member States can request further information or documentation to be submitted by the applicant. Therefore, after approval of the MRP-variation, a compiled variation application dossier including all subsequent delivered documentation can be submitted for the national duplicate. This ensures that the dossier of both medicinal products will be kept harmonised.

In addition to the variations, Follow-up Measures (FUMs) must be considered. As explained in this master thesis, in case of disagreement during the Mutual Recognition Procedure, a CMDh Referral meeting can be set up to reach agreement (see section 5.3 “CMDh Referral”). In order to obtain Marketing Authorisation, the applicant may give a commitment during this meeting that he will submit post-authorisation data on Module 3 (quality), Module 4 (preclinic) or Module 5 (clinic). These post-authorisation commitments can be Follow-up

Measures (FUMs) which have to be handled separately to the variations system. Therefore, they have their own series of sequential numbers so as not to be confused with the variations system. However, it is possible that a Competent Authority requests the submission of a variation after evaluation of a Follow-up Measure.⁶⁵ Furthermore, in urgent matters and after consultation with the Reference Member State, it can be considered appropriate to submit a variation that results from the fulfilment of the Follow-up Measure at the same time of the submission of the FUM to minimise the required processing time.⁸⁰

7. Discussion with regard to current pharmaceutical legislation

Within this master thesis, regulatory strategies and potential challenges during a Mutual Recognition Procedure (MRP) with 12 CMSs have been examined. Therefore, it was appropriate within this master thesis to subdivide the approval procedure into three parts (before, during and after authorisation via MRP) and to identify the critical aspects, taking current pharmaceutical legislation also into account. The following critical aspects that should be subject to a careful preparation have been identified:

Before Authorisation via MRP

- Clear responsibility assignment between applicant and consulting company
- Clarification whether further consulting companies or local operating companies are involved and responsibility assignment, if applicable
- Preparation of the dossier considering specific guidelines for biological medicinal products and conducting a new Readability User Testing, if required
- Choice of the Concerned Member States taking into account publicly available information regarding previous experience of the Member States within MRPs
- Evaluation of the national requirements of each Member State, such as payable fees
- Choice of the submission date of the application
- Scientific and procedural advice by the PEI and maybe by other NCAs or CHMP/EMA

During Authorisation via MRP

- Cooperativeness for dialogue with the RMS at all stages
- Evaluation of the national requirements of each Member State, such as the requirement of additional paper copies as well as the eCTD submission
- Contact with the RMS to start the procedure and CMSs to provide response documents
- In case of disagreement, achieving a positive outcome with the aid of a Break-out session, CMDh Referral procedure and CHMP Arbitration procedure, respectively
- Submission of high quality national translations of the approved harmonised informative texts during the national Marketing Authorisation step and further discussion with the NCAs

After Authorisation via MRP

- Application for batch release to the PEI and, if necessary, initiation of a variation procedure to comply with an update of the relevant Monograph of the Ph. Eur.
- Discussion of a variation plan with the RMS with regard to the new Variation Regulation EC/1234/2008: Possibilities for Grouped applications and Worksharing procedures
- Application for a Common Renewal Date and harmonisation of the PSUR submission cycles
- Maintaining the Marketing Authorisation: notifications with regard to the “Sunset Clause”, submission of renewal, variations, Follow-up Measures and documentation related to pharmacovigilance in order to comply with the legislation and scientific progress
- Possibility for withdrawal of single Marketing Authorisations

It was presented that a consulting company could act as an interface between applicant and Competent Authority and can support the applicant during the Mutual Recognition Procedure. In advance, a clear responsibility assignment must be defined clarifying the tasks for which the consulting company is engaged. The DRAM of the consultancy could manage meetings, such as a Scientific Advice meeting and could establish a good communication practice with the RMS. Furthermore, it is possible to let him prepare all scientific documentation and response documents during the procedure. However, not all consultants are able to provide this service. If these documents are written by the applicant, it could be agreed that the DRAM of the consulting company reviews the documentation prior to submission. Such a

review could ensure that response documents are accurate, appropriate and do not miss the point. However, if further consultants or Local Operating Companies (LOCs) are involved, it is a challenge to organise the communication channel so that there is only one contact person for the authorities and a clear responsibility assignment. Furthermore, limits for a consulting company can arise due to a lack of integration in company-internal structures.

8. Conclusion and Outlook

The aim of this master thesis was to examine how a biological medicinal product can be approved during a Mutual Recognition Procedure (MRP) with Germany acting as Reference Member State (RMS), as well as how this approval procedure could be organised and backed up by a consulting company. Within this master thesis, the critical aspects of a Mutual Recognition Procedure (MRP) regarding the case study have been elaborated and were further discussed in section 7. “Discussion with regard to the current pharmaceutical legislation”. As a conclusion, it can be stated that an experienced external service provider can help to organise a well-structured procedure by offering concerted assistance and knowledge to each of these critical aspects. In particular, the preparation of Module 1 “Administrative, regional or national information” should be focused by a consulting company with expertise in several approval procedures, as Module 1 requires thorough knowledge of the national requirements in each Concerned Member State. A constant cooperation towards dialogue with the RMS helps to achieve a positive outcome of the MRP.

As mentioned in this master thesis, biological medicinal products, such as Advanced Therapy Medicinal Products, have an immense potential for patients and the pharmaceutical industry. Their manufacturing is a highly specialised process with complex methodologies. Therefore, their development requires extended research and worldwide knowledge exchange. To make these medicinal products available to as many patients as possible, all biological medicinal products that fall within the Annex of Regulation EC/726/2004 (such as developed by biotechnological processes using recombinant DNA) are compulsory to be authorised via the Centralised Procedure.

With regard to the future, it can be stated that the patent protection of many biological medicinal products has expired or will expire soon. This allows the approval of similar biological medicinal products, also called biosimilars. Examples of these are biosimilar

versions of epoetins used in treatment of anemia. In order to cope with the increasing impact of biosimilars on the European market, the Biosimilar Medicinal Products Working Party (BMWP) was established at the European Medicines Agency (EMA). Tasks of the BMWP are the preparation of guidelines and to give advice on the required comparability studies.⁸¹

As with other biotechnology products, it is mandatory for biotechnology-derived biosimilars to use the Centralised Procedure for a Marketing Authorisation Application. However, biosimilars that do not fall under the above-mentioned Annex of Regulation EC/726/2004 may be authorised via other approval procedures (National, Mutual Recognition or Decentralised Procedure).²⁴ Therefore, the following may be interesting topics to be discussed in future master theses:

- Approval of a biosimilar via the Mutual Recognition Procedure - comparison with the approval of a biosimilar via the Centralised Procedure
- Approval of a biosimilar via the Mutual Recognition Procedure - comparison with the approval of a biological medicinal product (without a reference product) in an MRP

In the last case, the need for an EU Risk Management Plan (RMP) could be discussed in detail, as it is strongly recommended within the application for a new biosimilar.⁸²

In the future, an interesting focus for consulting companies within the area of biological medicinal products could be to specialise in approval procedures for biosimilars. This could include the preparation of the Risk Management Plan or leading Scientific Advice meetings dealing with the Risk Management System and the design of comparability studies.

9. Summary

Biological medicinal products can be used to treat many diseases and are of a great potential for patients and the pharmaceutical industry. Their definition is given in Part I of Annex I of Directive 2001/83/EC. For biologicals, special legal rules apply due to their complexity and impact on public health. In the future, revolutionary treatments for diseases, such as Alzheimer's, may be offered by Advanced Therapy Medicinal Products (ATMPs) using gene therapy, somatic cell therapy or tissue engineering. Biological medicinal products that fall

within the Annex of Commission Regulation (EC) No 726/2004 “Medicinal products to be authorised by the Community” (such as developed by biotechnological processes using recombinant DNA) must be authorised via the Centralised Procedure (CP). This approval procedure leads to one Marketing Authorisation that makes the medicinal product available to patients and healthcare professionals all over the European Union. However, biological medicinal products that do not fall under the above-mentioned Annex can also be approved by a purely National Procedure (NP), a Mutual Recognition Procedure (MRP) or a Decentralised Procedure (DCP).

This master thesis provides an overview on how a biological medicinal product can be approved during a Mutual Recognition Procedure with Germany as Reference Member State (RMS) and with the Paul-Ehrlich Institute (PEI) as Competent Authority. In order to provide clarity, a fictional case of approving an allergen product is studied. Furthermore, it is discussed how such a large project can successfully and efficiently be managed from a consulting company’s point of view. Particular attention has been paid to the responsibility assignment between the applicant and the consultant required for such a project.

In its first part, this master thesis provides a brief introduction and gives general information about requirements to biological medicinal products, the conduction of a Mutual Recognition Procedure, and the role of a consulting company within an approval procedure. In the second part, the key data for the case study are mentioned. To identify possible regulatory strategies and critical aspects with regard to the case, the main part is subdivided into before, during and after authorisation via MRP. Therefore, the planning prior to submission of the application dossier, as well as the requirements following receipt of the approval is discussed. Within each subdivision focus is laid on important challenges, such as Scientific Advice meetings (to discuss the approval strategy with the authorities), an Article 29 CMDh Referral (to solve a disagreement between the Member States in case of a raised Potential Serious Risk to Public Health) and the batch release procedure (in Germany, biological medicinal products, such as allergen products, that are manufactured in batches require official batch control and batch release by the Paul-Ehrlich Institute). Finally, this thesis concludes with a discussion and an outlook. The outlook deals with a field of increasing importance: the approval of similar biological medicinal products, the so-called biosimilars according to Article 10(4) of Directive 2001/83/EC.

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Annexes

Annex 1 Map of the European Union



(Source: http://europa.eu/abc/maps/index_en.htm⁸³)

Annex 2 Draft Letter of Authorisation

To whom it may concern

POWER OF ATTORNEY

This is to confirm that

<Applicant> herewith authorises

<name and address of consulting company>

to act on behalf in all matters related to proceedings and correspondence with regard to the Mutual Recognition Procedure <MRP-number> for the following medicinal product:

<name of the medicinal product>.

Place, Date

Name, Function, Signature

Annex 3 Examples of Additional Data

Germany

**ANLAGE ZUM ZULASSUNGSANTRAG BEI SERA, IMPFSTOFFEN,
BLUTZUBEREITUNGEN UND TESTALLERGENEN**
ANNEX TO APPLICATION FOR SERA, VACCINES, BLOOD PRODUCTS AND ALLERGENS

**ERKLÄRUNG ÜBER DIE PRODUKTIONS-RÄUME UND
BESICHTIGUNGSERLAUBNIS**
(§ 25 ABS.8 AMG)

DECLARATION CONCERNING MANUFACTURING SITE AND PERMISSION FOR INSPECTION:

Sind mehrere Hersteller an der Herstellung und Prüfung des Arzneimittels beteiligt, ist die Erklärung sämtlicher Hersteller vorzulegen.

In case that different manufacturers are involved in the manufacture and testing of the medicinal product each of them shall present a declaration.

Erklärung, Lageplan und Raumaufteilungsskizze beifügen.

Attach declaration, rough layout of premises and rooms.

Der Hersteller des Arzneimittels versichert, dass Beauftragte des Paul-Ehrlich-Instituts die Prüfungen beim Hersteller beobachten und dabei die Betriebs- und Geschäftsräume zu den üblichen Geschäftszeiten betreten und in diesen Besichtigungen vornehmen können.

The manufacturer of the medicinal product confirms that persons commissioned by the Paul-Ehrlich-Institute may observe the tests carried out by the manufacturer and may enter the manufacturing site including office rooms for inspection during usual business hours.

Ein Lageplan und eine Raumaufteilungsskizze liegt bei.
Rough layout of premises and rooms is attached.

Ort, Datum
Place, date

Funktion und Unterschrift des Herstellers
function and signature of the manufacturer

(Source: Paul-Ehrlich-Institut: "Anlage zum Zulassungsantrag bei Sera, Impfstoffen, Blutzubereitungen und Testallergenen" / Annex to application for sera, vaccines, blood products and allergens, 04/2003-1³⁸)

France

FORM to fill in and to append to any correspondance or submission In the context of MA		
NAME OF THE PRODUCT :		
NAME OF THE PHARMACEUTICAL COMPANY :		
Contact person :		
TYPE OF PROCEDURE <i>(tick the relevant box)</i>	Procedure number <i>(if necessary)</i>	NL (ou EH) number <i>(if known)</i>
<input type="checkbox"/> Centralised <input type="checkbox"/> Mutual recognition (MR) <input type="checkbox"/> National with a view of future MR <input type="checkbox"/> National		
TYPE OF DOSSIER <i>(tick the relevant box)</i>		
<input type="checkbox"/> New application <input type="checkbox"/> Type I therapeutic variation <input type="checkbox"/> Type II therapeutic variation <input type="checkbox"/> Type I pharmaceutical variation <input type="checkbox"/> Type II pharmaceutical variation <input type="checkbox"/> MA transfer <input type="checkbox"/> Change of company name – address of the holder <input type="checkbox"/> Change of distributor <input type="checkbox"/> DMF (Drug Master File)	<input type="checkbox"/> Five-yearly renewal <input type="checkbox"/> Two-yearly renewal <input type="checkbox"/> Specific obligation – annual reevaluation <input type="checkbox"/> Follow up measure <input type="checkbox"/> Pharmacovigilance reports <input type="checkbox"/> Recours gracieux <input type="checkbox"/> Homeopathic registration <input type="checkbox"/> Other (specify) :	
<input type="checkbox"/> Additional documentation within the framework of a mentioned above procedure Specify :	Name of the person in charge of the dossier at l’Afssaps (if known)	
<input type="checkbox"/> Written response to a “contradictory” procedure within the framework of a mentioned above procedure Specify :		
<input type="checkbox"/> Dossier requested by the person in charge of the dossier at l’Afssaps		
TYPE OF PRODUCT <i>(tick the relevant box)</i>	FEES <i>(tick the relevant box)</i>	
<input type="checkbox"/> Chemical <input type="checkbox"/> Biological <input type="checkbox"/> Generic <input type="checkbox"/> Radio-pharmaceutical <input type="checkbox"/> Homeopathic <input type="checkbox"/> Herbals, herbal medicines <input type="checkbox"/> Selfmedication <input type="checkbox"/> Others (specify) :	<input type="checkbox"/> Cheque <input type="checkbox"/> Bank transfer (specify the name of the bank and the date of the transfer) :	
	If the fees are paid by bank transfer, include at least one of the NL numbers (if known) or failing that, the name of the product, on the transfer slip.	
Dossier to be sent to AFSSAPS –DEMEB – Unité AMM Logistique 143/147 Boulevard Anatole France 93285 Saint-Denis Cedex FRANCE		

January 2003

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(Source: AFSSAPS, Notice to Applicants for Marketing Authorisations of Medicinal Products for Human Use including “Form to fill in and to append to any correspondence or submission in the context of MA”, January 2003³⁹)

Poland

Draft statement by the applicant that he will submit samples of the medicinal product on request of the Polish Agency:

To whom it may concern

The applicant will submit samples of *<name of the medicinal product>* on request of the Polish National Competent Authority.

Place, Date

Name, Function, Signature

Annex 4 Example of a History of Sequences (Tracking Table)

Sequence	Submission description	RMS	CMSs – First Wave											
		DE	AT	BE	CY	CZ	DK	FI	FR	NO	PL	PT	SE	UK
0006	Follow-up Measure (Quality): Annual Stability Report	Nov 10	Nov 10	Nov 10	Nov 10	Nov 10	Nov 10	Nov 10	Nov 10	Nov 10	Nov 10	Nov 10	Nov 10	Nov 10
0005	Change to comply with an update of the relevant Monograph of the Ph. Eur.	Dec 09	Dec 09	Dec 09	Dec 09	Dec 09	Dec 09	Dec 09	Dec 09	Dec 09	Dec 09	Dec 09	Dec 09	Dec 09
0004	D90 Final agreed Product Information	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09
0003	D85-90 Responses to Questions	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09
0002	D60 Responses to Questions	Sept 09	Sept 09	Sept 09	Sept 09	Sept 09	Sept 09	Sept 09	Sept 09	Sept 09	Sept 09	Sept 09	Sept 09	Sept 09
0001	Validation update (All)	Dec 07	May 09	May 09	May 09	May 09	May 09	May 09	May 09	May 09	May 09	May 09	May 09	May 09
0000	Initial Marketing Authorisation Application	Dec 07	May 09	May 09	May 09	May 09	May 09	May 09	May 09	May 09	May 09	May 09	May 09	May 09

Note: This Tracking Table is placed as an Annex to the Cover letter within the “common” file (name: common-cover-tracking.pdf).⁵²

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

Berlin, 20.04.2011

Kristiane Kempny