Biologicals and Biosimilars

Differences and implementation of the regulatory requirements in the European Union versus those in the United States with special consideration and analysis of the implementation and improvement of safety standards for biosimilar products

Dissertation

zur

Erlangung des Doktorgrades (Dr. rer. nat.)

der

Mathematisch-Naturwissenschaftlichen Fakultät

der

Rheinischen Friedrich-Wilhelms-Universität Bonn

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Bonn 2017

Die vorliegende Arbeit wurde in der Zeit vom Februar 2014 bis April 2017 unter der Leitung von Herrn Prof. Dr. Harald G. Schweim am Lehrstuhl für Drug Regulatory Affairs des Pharmazeutischen Instituts der Rheinischen Friedrich-Wilhelms-Universität Bonn angefertigt.

Angefertigt mit Genehmigung der Mathematisch-Naturwissenschaftlichen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn

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Tag der Promotion: 25.01.2018

Erscheinungsjahr: 2018

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Ort, Datum

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Acknowledgements

I would like to thank especially Professor Dr. Harald G. Schweim for his support and for allowing me latitude.
This dissertation would have not been possible without the patience and motivation of my husband Stefan. I would like to thank to my friend Jennifer Firth, she was always a grandiose teacher and a fantastic and admirable mentor to me. Jennifer, many thanks to you for your efforts and valuable support over the many years we have known each other.

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List of Abbreviations

ADCC	Antibody-dependent cell-mediated cytotoxicity (Fc-associated function)
AMG	Arzneimittelgesetz (German Drug Law)
ANDA	Abbreviated New Drug Application
ANX	Appendix II condition
BfArM	Federal Institute for Drugs and Medical Devices
BIAM	Biosimilar Initial Advisory Meeting
BLA	Biologics License Application
BPD	Biosimilar Product Development
BsUFA	Biosimilar User Fee Act
BWP	Biologics Working Party
CAGR	Compound Annual Growth Rate
CAT	Committee for Advanced Therapies
CBER	Center for Biologics Evaluation and Research
CDC	Complement-dependent cytotoxicity (Fc-associated function)
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CMC	Chemistry, Manufacturing, and Controls
CMS	Concerned Member State
COMP	Committee for Orphan Medicinal Products
CP	Centralized Procedure
CSTR	Continuous stirred-tank reactor
CT	Clinical Trial
C-terminus	Carboxyl-terminus (The end of an amino acid chain terminated by a free carboxyl group (-COOH))
CTFG	Clinical Trials Facilitation Group
CVMP	Committee for Medicinal Products for Veterinary Use
DNA	Desoxyribonucleic acid
DCP	Decentralized Procedure
EC	European Commission
EDQM	European Directorate for the Quality of Medicines & HealthCare
EEA	European Economic Area
EEC	European Economic Community

ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EPAR	European public assessment reports
ERMS	European Risk Management Strategy
EU	European Union
Fab	Antigen binding (Fab) fragment
Fc	Fragment crystallizable
(F)FD&C Act	(Federal) Food, Drug and Cosmetic Act
FDA	Food and Drug Administration
FUMs	Follow-Up Measures
GCP-V	Good Clinical Practice-Verordnung (Provision)
GDUFA	Generic Drug User Fee Amendments
GKV	Gesetzliche Krankenversicherung (Spitzenverband) (statutory health insurance)
GMO	Genetically modified organism
GMP	Good Manufacturing Practice
GxP	Good x Practice (x is for e.g., Distribution; Clinical; Manufacturing; Laboratory)
HMPC	Committee on Herbal Medicinal Products
ICH	International Council on Harmonization, formerly known as International Conference on Harmonization
ICSR	Individual Case Safety Report
IMPD	Investigational Medicinal Product Dossier
INN	International Nonproprietary Names
IND	Investigational new drug application
LEG	Legally binding measure
MA	Marketing Authorization
MAA	Marketing Authorization Applicant
mAbs	Monoclonal Antibodies
MAH	Marketing Authorization Holder
MEA	Additional pharmacovigilance activity in the Risk-Management Plan
MRP	Mutual Recognition Procedure
N- terminus	NH2-(amine)-terminus (The start of a protein or polypeptide terminated by an amino acid with a free amine group (-NH2))
NCA	National Competent Authority
NCE	New Chemical Entity
NDA	New Drug Application
OECD	Organization for Economic Co-operation and Development

PAES	Post-authorization Efficacy Study
PAMs	Post-authorization Measurements
PASS	Post-authorization Safety Study
PDCO	Pediatric Committee
PDUFA	Prescription Drug User Fee Act
PEI	Paul-Ehrlich-Institute
PHSA	Public Health Service Act
PRAC	Pharmacovigilance Risk Assessment Committee
REC	Recommendation
REMS	Risk Evaluation and Mitigation Strategies
RMS	Reference Member State
SARs	Suspected Adverse Reaction
SmPC	Summary of Product Characteristics
SOs	Specific Obligations
SUSARS	Suspected Unexpected Serious Adverse Reaction
TSE	Transmissible spongiform encephalopathy
US	United States
USA	United States of America
USAN	United States Adopted Name
USC	United States Code
USP	United States Pharmacopeia
USP-NF	United States Pharmacopeia and The National Formulary
WHO	World Health Organization

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1 Introduction

Manufacturers of medicinal products need to know and follow specific legal and regulatory requirements if they want to place their medicinal products on the European Union (EU) or United States of America (USA) market. In the EU, medicinal products shall be safe, effective and consistent in quality. [1] Medicinal products in the USA are required to be safe and effective for its intended use and additionally, with regard to biological medicinal products; scientific evidences must show that the manufactured product meets the determined requirements of safety, purity, and potency. [2] [3]

Additionally, for biosimilar products, the imitator products of the biological innovator products which are available after the biological innovator´s product patent has expired, the biosimilarity to the reference product, the biological innovator product, must be established in a comparable manner. Typically this is done through specific non-clinical and clinical testing as outlined in the applicable scientific guidance documents published by the regulatory authorities. In contrast to the biological innovator product, the marketing approval requirements for the biosimilar products are simplified in terms of reduced dossier requirements and the clinical study requirements are also simplified. [4]

Evidence that all these requirements are met must be submitted with the product application and will be reviewed during the applicable regulatory approval procedure. [5]

The EU and USA have their own distinct regulatory requirements and procedures that must be met prior to placing medicinal products on the market. These market-specific pre-authorization safety requirements include most importantly drug product-specific requirements to clinical and non-clinical testing. In addition, other general safety-relevant regulatory requirements and quality considerations impacting the safety profile of a biological or biosimilar medicinal product must be met prior to medicinal product gaining access to the market.

After the marketing approval has been granted for the desired market, there are market-specific post-authorization regulatory requirements. For example, extended monitoring requirements, post-authorization safety (PASS) or -efficacy studies

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[1] Regulation (EC) No 726/2004 "Whereas" chapter (14); OJ L 136, 30.4.2004, p. 1, Consolidated version 05.06.2013; http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

[2] 21 CFR §310.303(a); April 2014; https://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol5/pdf/CFR-2014-title21-vol5-chapI.pdf

[3] 42 USC §262(a)(2)C)(i); April 2015; http://uscode.house.gov/view.xhtml?req=%28title:42%20section:262%20edition:prelim%29%20OR%20%28granuleid:USC-prelim-title42-section262%29&f=treesort&edition=prelim&num=0&jumpTo=true

[4] ICH GCG ASEAN Training Workshop on ICH Q5C, 30-31 May 2011, Kuala Lumpur; Alberto Ganan Jimenez & Brigitte Brake; http://www.ich.org/fileadmin/Public_Web_Site/Training/ASEAN_Q5C_workshop_May_2011/SESSION_IVa_Biosimilars.pdf

[5] 21 CFR §601.2(a); April 2015; https://www.gpo.gov/fdsys/pkg/CFR-2015-title21-vol7/pdf/CFR-2015-title21-vol7-part601.pdf

(PAES), may have to be performed to further monitor and prove the ongoing safety and effectiveness of the approved medicinal product.

In addition to these requirements, various other safety-related regulatory requirements apply in both, the pre- and post-authorization phase. Examples include authority inspections, naming and labeling requirements, and variation reporting requirements.

All member states of the European Union are subject to the European Economic Area (EEA) law. On the European Union level the Regulation (EC) No 726/2004 and the Directive 2001/83/EC are the most essential and comprehensive regulations for medicinal products within the EU. The Regulation (EC) No 726/2004 covers the authorization and surveillance of safety of medicinal products. The Directive 2001/83/EC covers a broad range of requirements for all human medicinal products and it defines the essential requirements that must be met.

In addition to the applicable EU-Regulations and EU-Directives, EU-Decisions are also legally binding to the EU-member states. To complete the European pharmaceutical regulatory framework, several other instruments (e.g., Recommendations, Opinions, or European Medicines Agency (EMA) guidelines) which are not legally binding, are available for and applicable to medicinal products in the EU. [6]

In the USA, the Federal Food, Drug, and Cosmetic Act, (FD&C Act) is federal law and the basic regulation for medicinal products. The FD&C Act is enforced by the Code of Federal Regulations (CFR). These legally binding rules and regulations, also named administrative law, regulate most of the medicinal products under the FD&C Act. The regulations for the marketing approval of these, typically chemically synthesized products, are found in 21 CFR Parts 300 – 499. [7] In addition, certain biological medicinal products are also regulated thereunder.

As indicated, some biological medicinal products, e.g., products containing biotechnology-derived enzyme human Imiglucerase as active ingredient, are also subject to the FD&C Act. [8] These types of biological products gain their marketing approval through the “New Drug Application” (NDA) process like chemically-synthesized products. But many biological medicinal products (e.g., medicinal products containing the biotechnology-derived enzyme human Galsulfase as active ingredient or medicinal products containing biotechnology-derived monoclonal antibodies (mAbs) as active ingredient such as Infliximab) are not primary subject to the FD&C Act but rather to the Public Health Service Act (PHS Act). [9] [10] Section 351 of the PHS Act serves as the basic regulation for biological products which are

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[6] Procedure for European Union Guidelines and related Documents within the Pharmaceutical legislative Framework; Doc. Ref. EMEA/P/24143/2004 Rev. 1 corr; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004011.pdf

[7] Food and Drugs, Parts 200 – 499; PART 314; April 2014; https://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol5/pdf/CFR-2014-title21-vol5-chapI.pdf

[8] CEREZYME, (NDA) 020367; May 1994; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=browseByLetter.page&productLetter=C

[9] NAGLAZYME, (BLA) 125117; May 2005; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=browseByLetter.page&productLetter=N

[10] REMICADE, (BLA) 103772; August 1998; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=browseByLetter.page&productLetter=R

not regulated under the FD&C Act. [11] Products covered by the Public Health Service Act obtain marketing approval through the Biologics License Application (BLA) process. The Public Health Service Act is federal law and is enforced by the Code of Federal Regulations as well. The FDA regulations for marketing approval of these biological medicinal products are established in the 21 CFR Parts 600 – 680. [12] To complete the US-American pharmaceutical regulatory framework, several other instruments like FDA guidance documents which are not legally binding, are available for and applicable to medicinal products in the USA.

In addition to the EU- and US-market specific binding and non-binding regulatory requirements the overarching guidelines of the **I**nternational **C**ouncil on **H**armonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) are applicable to both markets as well. [13]

Both the EU- and the US-market have complex pharmaceutical legislation and various regulations. Opportunities for the improvement of safety standards are available in both markets; especially in the area of biosimilar products.

In the following, a regulatory overview is provided of how a biotechnology-derived medicinal product is brought to both, the EU- and the US-market. The applicable legislation and relevant scientific documents to identify safety relevant requirements is analyzed, and differences between both markets with respect to the identified safety standards, namely overall safety-related regulatory standards, clinical safety - and non-clinical safety requirements and quality considerations are critically examined. A special focus is made on [1] the information that is available for biosimilar monoclonal antibodies (mAbs), and [2] the overall improvement of safety standards for biosimilar products.

Within the introductory chapter, a scientific and regulatory overview is given that introduces in the regulatory framework and the complexity of biotechnology-derived medicinal products.

The main chapter identifies significant overall safety requirements established by legislation and gives attention to the specific safety requirements established in EMA- and FDA scientific guidance documents which were categorized into [1] overall safety-relevant regulatory requirements, [2] clinical safety and [3] non-clinical safety testing requirements and [4] quality considerations. The chapter analyzes the available information to the mentioned categories of safety standards for biosimilar products. Finally, potential improvements to the safety standards of biosimilar products are addressed.

The final chapter summarizes and discusses the most significant safety relevant facts and provides a conclusion and outlook.

[11] 42 USC § 262; April 2015; http://uscode.house.gov/view.xhtml?path=/prelim@title42/chapter6A/subchapter2/partF&edition=prelim

[12] Title 21 Food and Drugs Parts 600-799; April 2014; https://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol7/pdf/CFR-2014-title21-vol7.pdf

[13] About ICH, Steering Committee; http://www.ich.org/about/organisation-of-ich/steering.html

2 Historical background

This chapter introduces the biological medicinal products of today; starting with the historical beginning of the development of biotechnology through the development of the first biotechnology-derived medicinal products.

2.1 From the beginning of biotechnology to the first therapeutic monoclonal antibody

It all began with beer. The cradle of modern biotechnology is more than 6.000 years old and began when the Sumerian in Mesopotamia started brewing beer with sprouted grain and after fermentation obtained the first alcoholic beverage. The first beer recipes were documented 4.000 years ago and up to 20 different beer varieties were produced. [14] [15]

A couple of thousand years later, the medic Robert Koch (1843-1910) developed bacteriological techniques like culture plate technology with solid, transparent nutrient media, and the incubator. He also discovered the tuberculosis pathogen. [16] In parallel, the “Father of genetics" Johann Gregor Mendel (1822-1884), performed research in the field of genetics and formulated the rules of heredity. [17]

Then, in 1908, medic and Nobelist Paul Ehrlich (1854-1915) formulated the potential of antibodies and the concept of “magic bullets” during his cancer research work. He was searching for chemical substances with particular affinities for morbifical organisms, like the antitoxin-toxin (antibody-antigen) relationship, where the chemical substances would go directly to the organisms for which they are aligned. [18] An important method for the production of monoclonal antibodies was the hybridoma-technology developed by G. Köhler and C. Milstein in 1975. [15] [19] For further information please refer to **Appendix A.**

Of significant importance for the drug sector was the year 1977. Genentech, the pioneer biotechnology-company, produced the first human protein (Somatostatin) in E. coli bacteria. [20] [21] Later, in 1982, the same company produced the first recombinant DNA-derived human insulin which was licensed to Eli Lilly and received FDA approval in 1985 for the recombinant growth hormone Protropin®. [20] [21] In 1986, the murine Muromonab-CD3 (trade name Orthoclone OKT3®) by Janssen-Cilag received FDA approval; this was the worldwide first monoclonal antibody for therapeutic purpose and was intended to treat acute steroid-resistant rejection

[14] Frühgeschichte; February 2016; http://www.brauer-bund.de/index.php?id=21

[15] „Biotechnologie für Einsteiger“; Renneberg, Reinhard; Berkling, Viola; 2013; ISBN: 978-3-8274-3047-2

[16] Robert_Koch; https://de.wikipedia.org/wiki/Robert_Koch

[17] Gregor_Mendel; https://de.wikipedia.org/wiki/Gregor_Mendel

[18] Paul Ehrlich – Biographical; http://www.nobelprize.org/nobel_prizes/medicine/laureates/1908/ehrlich-bio.html

[19] Hybridom-Technik; https://de.wikipedia.org/wiki/Hybridom-Technik

[20] A History of Firsts; http://www.gene.com/media/company-information/chronology

[21] Genentech; https://de.wikipedia.org/wiki/Genentech

reactions. [22] For more information on the historical development of biotechnology, please refer to **Appendix B.** Currently, monoclonal antibodies are produced by recombinant methods using the DNA cloning in expression systems as explained in **Appendix C** in which antibodies are produced in-vitro in bacteria- or cell cultures and selected by phage-display-screening. [15]

Major developments in production techniques and scientific methods resulted in pharmaceutical achievements. Since the first mAb-approval in 1986, many other biotechnology-derived monoclonal antibodies have been developed and approved for a broad range of diseases. In Germany and the EEA 46 monoclonal antibodies have been approved as of February 12, 2016. [22] [23] According to the information of the organization Biotech within Research-Based Pharmaceutical Companies, known as vfa.bio, as of January 20, 2016, a quantity of 191 medicinal products, including biosimilar products, with 151 active substances have been approved in Germany that are genetically-engineered. Such products are also called biopharmaceuticals. [24] In the USA, 56 biological medicinal products obtained Biologics license (BLA) from the FDA between 2008 and 2015. [25]

[22] Muromonab-CD3; https://de.wikipedia.org/wiki/Muromonab-CD3

[15] „Biotechnologie für Einsteiger“; Renneberg, Reinhard; Berkling, Viola; 2013; ISBN: 978-3-8274-3047-2

[23] Monoklonale Antikörper; Februar 2016; http://www.pei.de/DE/arzneimittel/immunglobuline-monoklonale-antikoerper/monoklonale-antikoerper/monoklonale-antikoerper-node.html?gts=3257586_list%253Dtitle_text_sort%252Bdesc

[24] Zugelassene gentechnische Arzneimittel in Deutschland; Januar 2016; http://www.vfa.de/de/arzneimittel-forschung/datenbanken-zu-arzneimitteln/amzulassungen-gentec.html

[25] NDA and BLA Calendar Year Approvals; (February 2016; 2014 and older reports are in the FDA Archive) http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm373413.htm

3 Meanings and exemptions

This chapter describes the term safety standards for biological medicinal products and provides information on exempted biological medicinal products.

3.1 Meaning of the term safety standards

Safety standards are established in both the EU and the USA in the form of requirements and considerations established by legislation, regulation and regulatory and scientific guidance documents which apply to a medicinal product during the different authorization phases. The pre-authorization phase occurs before a biological medicinal product gains market access; the post-authorization phase occurs after the medicinal product has successfully obtained marketing approval. Some safety requirements such as the Good Manufacturing Practice (GMP) apply in both phases, pre- and post-authorization.

The term safety standard relates to the safety relevant regulatory and scientific requirements that must be met prior and within the regulatory approval process of biotechnology-derived drug products in order to gain marketing approval and post-authorization. Some post-authorization safety requirements, like the extended monitoring and post-authorization studies, may apply only to certain specific biotechnology-derived products such as to novel active substances, others may be applicable to all marketed medicinal products (e.g., reporting requirements). To receive marketing approval, the safety, efficacy and quality of a biotechnology-derived drug product must be demonstrated. In addition, for biosimilar products, biosimilarity to the reference product, the biological innovator product, must be established in a comparable manner. Typically this is done through specific non-clinical and clinical testing as outlined in the applicable scientific guidance documents about non-clinical, clinical and quality issues, published by the EMA and FDA, the regulatory authorities of the European Union and the USA. Overall safety relevant regulatory requirements are established by legislative documents and may also potentially impact the safety of biotechnology-derived products.

3.2 Exemptions

Immunological medicinal products, (e.g., vaccines, toxins, serums, allergen products), human blood and plasma products, (e.g., clotting factors), advanced therapy medicinal product like gene – and cell therapeutics are exempted and not discussed. Further, therapeutic synthetic peptide products of 40 or fewer amino acids covered by the US PHS Act and biotechnology-derived products covered under the FD&A Act are not considered.

4 Definitions

This chapter defines the terms “biotechnology-derived”, “medicinal product”, “biological product” and “biosimilar” within the European Union and the USA. Please note, the term biotechnology-derived product refers to both, the biological innovator product and the biosimilar product. All definitions of this chapter can be found cited in **Appendix D.**

4.1 Biotechnology-derived

Biotechnology-derived medicinal products are products like high-molecular-weight proteins and polypeptides which themselves or their active substance is produced by biotechnological production processes. These biotechnology-derived products are typically produced by genetically-engineered living systems. In the European Union, the concerned products are mentioned in Article 3(1) of Regulation (EC) No 726/2004 and defined in point 1 of the Annex of the mentioned Regulation and include for example products developed by recombinant DNA technology and by hybridoma and monoclonal antibody methods. [26]

Within the USA, the considered biotechnology-derived products are covered by the Public Service Health Act and they are defined by the regulations of the Food and Drug Administration as “specified biological products”. [27] Those products include for example therapeutic recombinant DNA-derived products and monoclonal antibodies for in vivo use.

4.2 Definitions in the European Union

The Directive 2001/83/EC provides the regulatory basis and legal definition of the term “medicinal product”. [28]

The term “biological” legally is defined in Appendix I of Directive 2001/83/EC and the regulatory basis is provided there. The active substance of biological products is a biological substance that comes from a biological source. [29]

The term “biosimilar” is defined in the EMA similar products guidance document in section 3.1. A biosimiliar product contains a version of the active substance of an EEA authorized biological innovator product and therefore, is biosimilar and not bio-identical to that reference product. Similarity of the biosimilar product to the

[26] Regulation (EC) No 726/2004 Article 3(1) and Point 1 of the Annex; OJ L 136, 30.4.2004, p. 1, Consolidated version 05.06.2013 ; http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

[27] 21 CFR §601.2(a); April 2014; http://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol7/pdf/CFR-2014-title21-vol7-part601.pdf

[28] Directive 2001/83/EC Title I, Definitions of Article 1; OJ L 311, 28.11.2001, p. 67, Consolidated version 16/11/2012 ; http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[29] Directive 2001/83/EC Part I, Appendix I, section 3.2.1, subsection 3.2.1.1(b); OJ L 311, 28.11.2001, p. 67, Consolidated version 16/11/2012; http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

reference product must be established by comparative testing regarding the quality properties, biological activity, safety and efficacy. [30]

4.3 Definitions in the USA

The definition of “drug” in the Federal Food, Drug and Cosmetic Act (FFD&C Act) also applies for biological products which are covered under the PHS Act. [31] The PHS Act provides the regulatory basis and legal definition of the term “biological product” and “biosimilar”. [32] The term “biological product” comprises various biological sources such as virus, toxin, blood, proteins or trivalent organic arsenic compounds, etc. The term “biosimilar” refers to a biosimilar product that is highly similar to a FDA approved biological innovator product and for which no clinically meaningful differences were observed between the biosimilar product and the reference product with regard to its safety, purity, and potency.

[30] Guideline on similar biological medicinal products; CHMP/437/04 Rev 1, 23 October 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

[31] 21 USC §321(g); April 2015; http://uscode.house.gov/view.xhtml?req=%28title:21%20section:321%20edition:prelim%29%20OR%20%28granuleid:USC-prelim-title21-section321%29&f=treesort&edition=prelim&num=0&jumpTo=true

[32] 42 USC §262 (i)(1), 42 USC §262 (i)(2)(A),(B); April 2015; http://uscode.house.gov/view.xhtml?req=%28title:42%20section:262%20edition:prelim%29%20OR%20%28granuleid:USC-prelim-title42-section262%29&f=treesort&edition=prelim&num=0&jumpTo=true

5 Current status and market figures for biotechnology-derived products

The chapter describes the importance of biotechnology-derived products in medicine, their impact on the health expenses and market trends. Please note, the overall term biopharmaceutical products refer to all recombinant-DNA derived medicinal products.

5.1 Current market figures and future trends

The range of the recombinant DNA-derived medicinal products is huge and includes, for example [1] hormones (e.g., insulin, erythropoietin); [2] monoclonal antibodies like the biologic response modifiers (BRMs); [3] recombinant clotting factors; [4] enzymes such as α-Glucosidase; and [5] diverse recombinant vaccines e.g., against Hepatitis B and cervical cancer. The therapeutic application of these products is multifarious and covers a broad range of diseases such as auto-immune generated diseases like rheumatoid arthritis, multiple sclerosis and diabetes; types of cancer like Non-Hodgkin-Lymphoma; as well as metabolism- and clotting disorders and osteoporosis. [24]

It is very likely that the market of biopharmaceutical products (biological products including mAbs, other recombinant DNA-derived proteins; and biotechnological and genetically engineered vaccines) will continue to grow in the future. According to the information provided in the vfa.bio 10th Biotech Report summarizing the development of the German medical biotechnology, 155 biopharmaceutical products were approved in 2005 compared to 226 products in 2014. [33] Simultaneously, biopharmaceutical sales rose from 2.6 billion Euros in 2005 to 7.5 billion Euros in 2014. [33] Biopharmaceutical sales rose by 7% in 2014 from 2013 in real terms compared to the total pharmaceutical market with a grow rate of 6.6% in 2014 from 2013 in real terms. The percentage of Biopharmaceuticals in the pharmaceutical market grew from 21.4% to 22.0%. [33]

With respect to monoclonal antibody products, the vfa.bio 10th Biotech Report describes an increasing number of mAbs in the pipeline; in 2005 there were 79 mAbs and in 2014 there were 357 mAb products. [33] In addition, the biopharmaceutical share of the market rose from 12% in 2005 to 22% in 2014. [33]

The US-market is the market leader in the production of biopharmaceuticals followed by Germany. [34] [35] According to the forecast information of IMS institute

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[24] Zugelassene gentechnische Arzneimittel in Deutschland; Januar 2016; http://www.vfa.de/de/arzneimittel-forschung/datenbanken-zu-arzneimitteln/amzulassungen-gentec.html

[33] Medizinische Biotechnologie in Deutschland 2005 - 2015 - 2025: Bedeutung für Patienten, Gesellschaft und Standort; 10.Biotech-Report ; June 2015; http://www.vfa-bio.de/download/bcg-report-2015.pdf

[34] Biopharmazeutika - Hightech im Dienst der Patienten; October 2010; http://www.vfa-bio.de/vb-de/aktuelle-themen/branche/biopharmazeutika-hightech-im-dienst-der-patienten.html

[35] Global Outlook for Medicines Through 2018; Murray Aitken; Michael Kleinrock; Jennifer Lyle; Deanna Nass; and Lauren Caskey from imsHealth; November 2014; http://www.imshealth.com/en/thought-leadership/ims-institute/reports/global-outlook-for-medicines-through-2018#ims-form

for healthcare informatics (IMS Health™) published in November 2014, it is anticipated that the total global expenses for medicinal products will increase to $1.3 Trillion from 2014 to 2018 (an increase of approximately 30% from 2013), and that specialty drug products, e.g., biotechnology-derived products, will constitute 40% of the total global growth. [35]

According to Transparency Market Research, another market research company, the US biopharmaceuticals market value was estimated with US$ 90 billion in 2012 and is expected to grow at a compound annual growth rate (CAGR) of 11% by 2018 which means further expansion of the biopharmaceutical market. [36] This is also supported by the fact that while the FDA licensed only four biological products via Biologics License Application (BLA) approval in 2008, they licensed 11 in 2014 and 12 in 2015. [25] Information to increasing growth of the global biopharmaceuticals market is also provided in a global market study published by the company Persistence Market Research (PMR). Here, the value of the global biopharmaceuticals market was estimated with US$ 161,851.6 billion in 2014 and is now expected to grow at a compound annual growth rate (CAGR) of 9.4% to achieve US$ 278,232.9 billion by 2020. [37]

Growth of the total US-pharmaceutical market is expected to be 5-8% compound annual growth rate (CAGR) through 2018 compared to the German market which is expected to be 2-5% CAGR while 1-4% CAGR is expected for the five EU countries Germany, France, Italy, U.K. and Spain together through 2018. [35] Global spending growth is expected to be 4-7% compound annual growth rate through 2018. [35]

While the value of the biopharmaceuticals market is steadily growing, the financial resources that the statutory health insurances (GKV) dedicate for prescribed biotechnology-derived products are also increasing. [38] According to information from the German Barmer Gmünder Ersatzkasse (Barmer GEK) annual report of 2015, 13% of drugs expenditures are spent for biopharmaceutical products with increasing trend. [39] Between the years 2013 - 2014, the Barmer GEK spent 39.2 % of their total expenses, which was 1.73 billion Euros, for 3.5 % of prescribed biological products. [39] Annual financial expenditures of 30 000 Euros and more per patient (e.g., Lenalidomid therapy for cancer treatment) for biological products are typical. [39] The high prices in the biological products sector are caused by their high

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[35] Global Outlook for Medicines Through 2018; Murray Aitken; Michael Kleinrock; Jennifer Lyle; Deanna Nass; and Lauren Caskey from imsHealth; November 2014; http://www.imshealth.com/en/thought-leadership/ims-institute/reports/global-outlook-for-medicines-through-2018#ims-form

[36] US Biopharmaceutical Market - Global Industry Size, Market Share, Smart Trends, Analysis And Forecast 2012 – 2018; http://www.transparencymarketresearch.com/us-biopharmaceutical-market.html

[25] NDA and BLA Calendar Year Approvals; February 2016; (2014 and older reports are in the FDA Archive); http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm373413.htm

[37] Global Market Study on Biopharmaceuticals: Asia to Witness Highest Growth by 2020; Years 2014-2020; May 2015; http://www.persistencemarketresearch.com/market-research/biopharmaceutical-market.asp

[38] Pressemitteilung; December 2015; http://presse.barmer-gek.de/barmer/web/Portale/Presseportal/Subportal/Laender/Einstieg-BaWue/Pressemitteilungen-Archiv/Archiv_202015/151230-arzneimittelreport-ulm/151230-pm-download,property=Data.pdf

[39] BARMER GEK ARZNEIMITTELREPORT 2015; Schriftenreihe zur Gesundheitsanalyse Band 32, Arzneimitteldaten aus den Jahren 2013 bis 2014 ; June 2015; https://www.barmer.de/blob/37954/60143006d7108440f02512a6a80fcaea/data/pdf-arzneimittelreport-2015.pdf

development- and manufacturing costs which are up to US$ 1.6 billion for novel biopharmaceuticals until market access is achieved. [40] [33]

Due to the high cost of biological products and the desire to widen patient access and choice, great hopes are being set in biosimilar products, the imitator products of the biological innovator products. Biosimilar products may access the market after the patent expiration of the first-in-market product that is intended to be used as reference product. The active substance of these imitator products may be a version of that of the reference product and therefore it is bio-similar but not bio-identical to those of the reference product. [30] While their production is also cost intensive as they are not as inexpensive to manufacture as most chemically-synthesized generic drugs; they tend to be cheaper than the biological innovator product. [41]

The first EMA approved biosimilar was Omnitrope® (Somatropin) in 2006, and the first EMA approved biosimilar monoclonale antibodies were Inflectra™ by Hospira and Remsima by Celltrion in June, 2013. [42] [43] Currently the EMA has approved 19 biosimilar products within the EEA region. [44] A list of EMA-approved biosimilar products and innovator biological products as of January 2016 is available on the vfa-bio website. [24]

In the US- market the first biosimilar product was approved by the FDA on July 24, 2014 (Zarxio by Sandoz, a Filigrastim preparation). [45] [46] Currently, there is one FDA approved biosimilar mAb product “Inflectra”. [47] And a few regulatory submissions have been accepted by the FDA for review. [48] [49]

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[40] The current State of Innovation in the Pharmaceutical Industry; Wilsdon, T; Attridge, J.; Chambers, G., Charles River Associate (CRA) International, June 2008

[33] Medizinische Biotechnologie in Deutschland 2005 - 2015 - 2025: Bedeutung für Patienten, Gesellschaft und Standort; 10.Biotech-Report ; June 2015; http://www.vfa-bio.de/download/bcg-report-2015.pdf

[30] Guideline on similar biological medicinal products; CHMP/437/04 Rev 1, 23 October 2014 ; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

[41] Kostenvorteil; Februar 2016; http://probiosimilars.de/biosimilars/kostenvorteil/

[42] Omnitrope somatropin Authorization details; EMEA/H/C/607; April 2006; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000607/WC500043689.pdf

[43] EMA Approves First MAb Biosimilars; July 2013; http://www.biopharma-reporter.com/Markets-Regulations/EMA-Approves-First-MAb-Biosimilars

[44] Originalpräparate und Biosimilars (zugelassen in der EU); Januar 2016; http://www.vfa.de/download/biosimilars-uebersicht-originalpraeparate.pdf

[24] Zugelassene gentechnische Arzneimittel in Deutschland; Januar 2016; http://www.vfa.de/de/arzneimittel-forschung/datenbanken-zu-arzneimitteln/amzulassungen-gentec.html

[45] FDA Accepts First Biosimilar Application Filed under Section 351(k) of the Public Health Service Act; Jula 2014; http://www.klgates.com/fda-accepts-first-biosimilar-application-filed-under-section-351k-of-the-public-health-services-act-07-28-2014/

[46] Court allows Sandoz to launch first US Biosimilar in September; Zachary Brennan; July 2015; http://www.biopharma-reporter.com/Markets-Regulations/Court-allows-Sandoz-to-launch-first-US-biosimilar-in-September

[47] FDA approves Inflectra, a biosimilar to Remicade; April 2016; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm494227.htm

[48] FDA accepts Sandoz regulatory submission for a proposed biosimilar etanercept; Novartis; October 2015; https://www.novartis.com/news/media-releases/fda-accepts-sandoz-regulatory-submission-proposed-biosimilar-etanercept

[49] Hospiras Remicade copycat up for review as US biosimilars March on; Dan Stanton; February 2015; http://www.biopharma-reporter.com/Markets-Regulations/Hospira-s-Remicade-copycat-up-for-review-as-US-biosimilars-March-on

6 Biological products and biotechnology-derived medicinal products

This chapter provides an overview to biological products, biosimilar products and the structural specialties and complexity of biotechnology-derived products that may explain their regulatory handling.

6.1 Biological products

The active substance of all biological products is of biological nature which comes from a biological source and this includes products like immunological medicinal products, human blood and plasma products, and advanced therapy medicinal products, which are exempted and not further and discussed. [28] Although many biological and biosimilar products are produced with biotechnological methods today, three examples for biological products which were produced with non-biotechnological methods in the past will be provided below to demonstrate the timely and financial effort their production has needed. The examples include biological products exempted in section 3.2.

- Clotting factor VIII

The genetic disease Hemophilia A affects only males. The defect leads to a shortage of the clotting factor VIII which causes that already a minor injury could lead to life-threatening bleeding. In the past, the clotting factor VIII was extracted from human donor blood. A bleeder needs a clotting factor VIII amount of 2 mg per week and about 6 litres of human donor blood contain only 1 mg of clotting factor VIII which means that 24 blood donors are necessary per week to provide the needed clotting factor assumed each donor gives 500 ml blood. [15] Beside of the huge production costs there are several health risks associated with this way of production such as serious virus infections with AIDS or Hepatitis. Currently, recombinant clotting factor VIII is biotechnologically produced e.g., in genetically-engineered Chinese Hamster Ovary (CHO) cells, and on market since 1992. [15] [50]

- Interferon

Another example is the production of Interferon. Interferon is a protein produced by the human body, and among other things, responsible to stimulate the immune system in order to defense viruses and tumor cells. Interferon was identified by A. Isaacs and J. Lindemann in 1957. In the 70s K. Cantell developed a technique to produce interferon from human blood by infecting leucocyte of human blood donors with a virus. Then, the interferon which was produced by the human cells was collected and purified. To produce 0,5 Gramm of interferon with this method, a

[28] Directive 2001/83/EC Title I, Definitions of Article 1; OJ L 311, 28.11.2001, p. 67, Consolidated version 16/11/2012 ; http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[15] „Biotechnologie für Einsteiger“; Renneberg, Reinhard; Berkling, Viola; 2013; ISBN: 978-3-8274-3047-2

[50] Rekombinante Blutgerinnungsfaktoren; https://de.wikipedia.org/wiki/Rekombinante_Blutgerinnungsfaktoren

volume of 50 000 litres of donor blood plasma was needed. [15] In 1979, C. Weissmann succeeded to produce interferon by bacterial synthesis in E. coli. In contrast, now a volume of only 10 litres bacteria culture solution were enough to produce 0,5 Gramm interferon. Since 1983 different types of biotechnology-derived interferon and recombinant interferon are available on market and used in various therapeutic areas such as autoimmune diseases, virus infections or cancer. [15] [51]

- Paclitaxel

Paclitaxel is an extract of the bark of the pacific yew tree and was identified in 1962 by A.S. Barclay and is used in the chemotherapeutic Taxol which was first approved by the FDA in 1992 for the therapy of metastatic ovarian. [52] The Paclitaxel is able to block cancer cells but is only in limited quantity available in one tree. The bark of 12 yew trees would be necessary to extract 1 Gramm of the active substance with the initial production process. [53] So, bark of hundred thousands of old and slow growing pacific yew trees would be needed for the extraction of the active substance to treat US-American patients with ovarian cancer for one year. [15] To save natural resources several researches were done and in 1992 a semisynthetic method developed by R. Holton was patented which used needles of the European yew tree. [15] Since 2002 it is possible to produce the active substance biotechnologically in fermenters by using cell cultures of the yew tree. [54] The Paclitaxel production in bacteria or yeast is still in research. [55]

Today, many biological innovator products and biosimilar products are produced by complex biotechnological genetically-engineered processes on the basis of biological living source materials, e.g., animal or plant cells, and microorganism such as bacteria or yeast. These biotechnology-derived products are complex in their molecular structure.

6.2 Biosimilar products

After the biological innovator´s product patent has expired biosimilar products may apply to gain market authorization. Biosimilar products are imitator products of the chosen reference biological innovator product, and contain a version of the active substance. Due to unavoidable minor differences in the production of biosimilar products (e.g., diversified production processes, differing production parameters or producing source organisms- or cell-lines), it is not possible to make biosimilar products bio-identical to their biological innovator products. Thus, the non-identical structure of the active substance of biosimilar products may lead to differences in strength with consequences to the dose needed for the same efficacy as the referenced innovator product has, or to a different retention time in blood; but also to

[15] „Biotechnologie für Einsteiger“; Renneberg, Reinhard; Berkling, Viola; 2013; ISBN: 978-3-8274-3047-2

[51] Interferone; https://de.wikipedia.org/wiki/Interferone

[52] Success story Taxol® (NSC 125973); December 2016; https://dtp.cancer.gov/timeline/flash/success_stories/s2_taxol.htm

[53] Paclitaxel; https://de.wikipedia.org/wiki/Paclitaxel

[54] Paclitaxel aus Fermentern; 2002, Ausgabe 34; http://www.pharmazeutische-zeitung.de/index.php?id=pharm5_34_2002

[55] Biologische Pharmaproduktion; Max-Planck-Gesellschaft, München, April 2015; https://www.mpg.de/9169009/biologische_pharmaproduktion

clinical safety relevant differences (e.g., differences in or as yet unknown unwanted adverse effects). [56] The EMA guidance document for similar products – non clinical and clinical issues mentions those differences in the qualitative or quantitative nature of product-related versions could impact biological functions of the biotechnology-derived product and may have an effect on immunogenicity and hypersensitivity potential. Thus, such potential should be evaluated in clinical studies as animal studies are not suitable to predict such potential. [57]

Therefore, it is of major importance to establish comparable biosimilarity from the proposed biosimilar product to the chosen reference product by demonstrating comparability of their quality attributes and biological activity, as well as clinical safety and efficacy. If differences between the proposed biosimilar product and the reference product are detected during testing, it must be demonstrated that these differences have no relevant impact to the biosimilar product clinical safety and / or its efficacy.

Theoretically, any biotechnology-derived product may be demonstrated to be biosimilar to a chosen reference product, especially highly purified products that can be thoroughly characterized. [30] However, in practice, the biosimilar approach is not feasible for all biotechnology-derived products. Not all products proposed to be biosimilar are physico-chemically and biologically characterizable to the extent needed to establish comparable biosimilarity between both products. For other biotechnology-derived products again, only little clinical and regulatory experience is available to use this approach. [30]

Many biosimilar products are intended for the long-term treatment of chronic diseases; but clinical safety studies conducted prior to authorization are normally not sufficient to detect and to identify rare adverse effects. Therefore, many biosimilar products are subject to an extended and strict pharmacovigilance course. Typically, during the biosimilar products post-approval phase, the marketing authorization holder (MAH) is required to closely monitor the clinical safety of the biosimilar product in a continuous fashion and also to evaluate the products benefit-risk-balance. [57] Additionally, post-authorization safety and / or efficacy studies may be necessary and more intensive monitoring and labeling may be required by regulatory decision.

6.3 Specialties of biotechnology-derived products

In contrast to chemically-synthesized products, biotechnology-derived products (e.g., mAbs, recombinant DNA-derived proteins) are manufactured using genetically-engineered living production systems in biotechnological manufacturing processes of high complexity. Three major facts can be identified for biotechnology-derived showing the differences to common medicinal drugs, and each fact may

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[56] Biopharmazeutika Hightech im Dienst der Patienten; vfa - Die forschenden Pharmaunternehmen, December 2010 http://www.vfa.de/download/broschuere-biopharmazeutika.pdf

[57] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev1, 18 December 2014 , http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf

[30] Guideline on similar biological medicinal products; CHMP/437/04 Rev 1, 23 October 2014, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

impact the final biological product. These three facts are: [1] the application of living and genetically-engineered production systems for production purpose; [2] the complexity of the biotechnological manufacturing process; and [3] the structural complexity of the manufactured biological product.

There are various living systems such as bacteria, yeast, animal or human cells, viruses, or transgenic animals or plants used as production systems for biological products. These living and genetically-engineered systems react very sensitively to variability in environmental parameters like temperature, ph- value, nutrient supply, or concentrations of oxygen or carbon dioxide gas; and to contamination like adventitious agents introduced from outside by accident into the bio-system, or any impurities from inside the bio-system itself arose from lysis of dead cells. Therefore, it is of high importance to adequately and continuously control the biotechnological manufacturing process conditions including the cell culturing process of the source material. Here, the inheritance of the living system should be known in terms of any possible prior contacts with viruses or any other contaminations. Uncontrolled process conditions may change cell functions or characteristics (e.g., protein synthesis, glycosylation's or cell metabolism) and this may lead to different product results than expected.

The manufacturing process provides a range of uncertainties and differences that may impact the biotechnology-derived product and its molecular structure, including its primary structure, any higher order structures, glycosylation's and other (post-translational) modifications, as well as product-related- and process-related impurities. Typically, the molecular conformation of a biological product protein is a three-dimensional structure (3D-structure) that results from molecule folding. Several interactions influence the folding of the molecule such as different types of bonding (e.g., amide bonding, disulfide bonding, hydrogen bonding) or other physicochemical interactions (e.g., van der Waals force, hydrophobic interactions). Proteins may be unstable in their molecular structure which leads to the circumstance that their molecular conformation can be impacted and shifted easily. This may happen by subtle environmental events such as varying temperatures, sheer forces, energy exposure (e.g., sunlight) or by minor changes to any process steps such as the used culture media, type of aqua or stirring rate in the fermenter. In consequence, the overall considerations regarding the manufacturing process should be comprehensive in nature and should include process steps like cultivation parameters and medium including starting / source material and raw materials, fermentation, purification, filtration, active substance, and final product.

The differences of biotechnology-derived products in comparison to chemically-synthesized products and the challenges of biotechnological manufacturing processes are recognized in published guidance documents by both, the FDA and the EMA. [58] [59]

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[58] Frequently Asked Questions About Therapeutic Biological Products, Question 10: How is the manufacturing process for a biological product usually different from the process for drugs?; July 2015; http://www.fda.gov/Drugs/DevelopmentApprovalProcess/%20HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm

[59] EU guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use; Ref. Ares(2012)778531 - 28/06/2012 ; http://ec.europa.eu/health/files/eudralex/vol-4/vol4-an2__2012-06_en.pdf

Resulting from interactive processes and other process influences (e.g., varying parameters, impurities) during the biotechnological manufacturing process or after, the produced biotechnology-derived product may vary in its complexity, structure and properties. These differences may be a result from amino acids modifications to the N-or C-terminus ends of the intact protein molecule; from diverse carbohydrate moieties attached to the protein (e.g., by post-translational glycosylation's) that resulting in protein heterogeneity or by modifications of any higher order structures.

Overall, any (post-translational) modifications or degradations of changing the protein structure, including modifications to the amino acid sequence, may raise clinical safety issues such as triggering immunogenicity. Immunogenicity is considered a significant clinical safety concern for biotechnology-derived products as it may cause a loss of efficacy or may lead to serious adverse events such as anaphylaxis or cytokine release syndrome. [60] [61] Other factors to be considered due to their role in inducing immune reactions include the final product formulation and packaging, protein aggregation; adduct generation and impurities. [61]

The most significant specifics of biotechnology-derived products are listed below:

- Large molecules of high complexity
- Typically high molecular weight
- Complex source/starting material and raw material
- Produced/synthesized in or extracted from living cell or microorganisms
- Many critical manufacturing process steps that are more challenging to control
- Multistep purification process aiming removal of a broad range of product – and process related impurities and adventitious agents
- Characterization of molecule structure less easily and limited due to high protein molecule variability, difficult to reproduce
- Molecular structure may remain partially unknown / incomplete defined, high complex and dynamic 3D- structure often instable and influenced by environmental parameters, posttranslational modifications likely, high natural and process induced variability of function and structure of the molecule
- Heterogeneous compositions, variants may be included
- Potentially immunogenic due to structural differences or alterations of the protein molecule, any impurities / adventitious agents, any environmental events, or formulation related issues

6.4 The manufacturing process of biotechnology-derived products

Biotechnology-derived products are typically produced by genetically-engineered living systems by means of genetically modifications to cell-lines or cell-constructs. There are various genetically-engineered living systems used as production systems (expression systems) for recombinant proteins such as bacteria, yeast, animal or

[60] Immunogenicity Assessment for Therapeutic Protein Products; Guidance for Industry, August 2015; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf

[61] Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins; EMEA/CHMP/BMWP/14327/2006 Rev1; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/10/WC500194507.pdf

human cells, viruses and even insect cell lines. [62] Also the use of transgene plants and transgene animals like goats is common in the production of biotechnology-derived products. [63] Typically, after the living organism (e.g., bacterial cells) has been genetically modified by inserting the necessary amino acid sequences into the host cell, the host cell can produce the desired protein. The most suitable genetically-engineered cell-line is then further processed in a biotechnological process of high complexity. The commercialized culturing of the cell-lines is typically carried out in large scale bio-reactors, also called fermenters. There are various types of bioreactors available that can be classified based on their mode of production; for example, batch process-, continuous process- and fed-batch (semi-continuous) process. The most established bioreactor-model is the continuous stirred-tank reactor (CSTR). [15] After cell-culturing and fermentation, the harvested proteins are purified and formulated into the final product.

The typical biotechnological production process can be separated into two main sections, the first step “up-stream” process followed by the second step “down-stream” process. [64] [65] This is visualized in *Figure 1*. It should be noted that any changes to the up-stream process steps (e.g., cell bank preparation or fermentation) may influence the downstream process steps such as production and purification, and ultimately influence the final product.

[63] EPAR ATryn antithrombin alfa; EMA/403685/2016, EMEA/H/C/000587, June 2016; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000587/WC500028255.pdf

[15] „Biotechnologie für Einsteiger“; Renneberg, Reinhard; Berkling, Viola; 2013; ISBN: 978-3-8274-3047-2

[64] Vorlesung „Biotechnisch hergestellte Arzneimittel“, Unterlagen zum Weiterbildenden Studiengang „Master of Drug Regulatory Affairs“; Folie 43 von 183, May 2012; Brake, Frau Dr. Brigitte

[65] Overview of Upstream and Downstream Processing of Biopharmaceuticals; Prof. Ian Marison; March 2016; http://www.engineersirelandcork.ie/downloads/Biopharmaceuticals%2020Jan09%20-%202%20-%20Ian%20Marison%20DCU.pdf

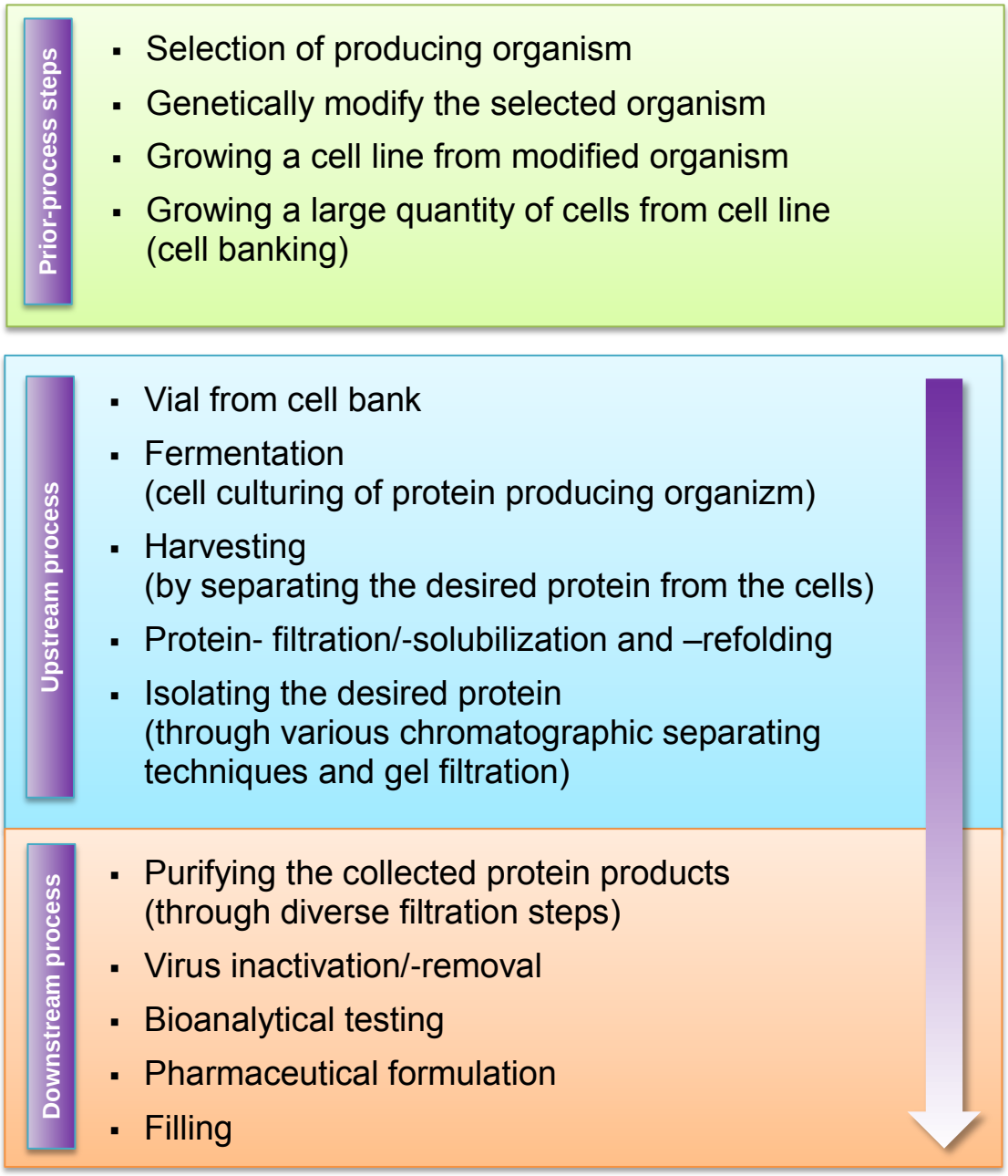

Figure 1 Major steps in production of biotechnology-derived products

Each process step must be well controlled because the entire production process defines the quality of the final product. The biotechnological production process must fulfill the strict requirements of the Good Manufacturing Practice (GMP) as described in the relevant ICH Q7 guideline at an early stage of the process as shown in *Figure 2* and presented in the ICH Q7 guideline. [66] The GMP requirements are further detailed in the CFR regulations in 21 CFR 210 and 211 and in the European GMP guidelines. [59]

[66] Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients; ICH Q7; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf

[59] EU guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use; Ref. Ares(2012)778531 - 28/06/2012; http://ec.europa.eu/health/files/eudralex/vol-4/vol4-an2__2012-06_en.pdf

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plants	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

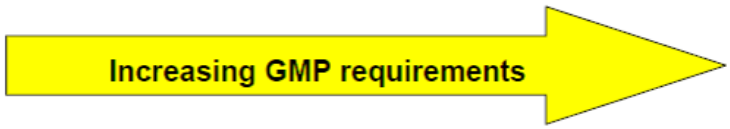

Figure 2 Application of GMP-requirements to active pharmaceutical ingredients

©by ICH [66]

[66] Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients; ICH Q7; November 2000; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf

7 The regulatory framework in the European Union and the USA

Within this chapter, information is provided on the regulatory environment, framework and information on the responsible regulatory authorities in the European Union and the USA.

7.1 Institutions and structures within the European Union

The European Union today consists of 28 sovereign and independent member states which together form a joint federation of countries. [67] The EU and Norway, Liechtenstein and Island constitute together the European Economic Area (EEA). The early structures of the European Union were established in 1950 by Belgium, France, Germany, Italy, Luxembourg and the Netherlands. [68] The joint federation of the member states of the European Union works in the following way; the member states delegate some of their powers, in terms of decision making, to the institutions of the European Union with the aim that decisions that are of interest for the European Union level, can be made democratically at that level. The three main institutions involved in EU legislation and their primary responsibilities are listed below: [69]

- The European Parliament: Represents the EU´s citizens and is involved in law-making procedures and acts;
- The European Council: Represents the governments of the individual member countries and is involved in law-making procedures and setting political orientation; and
- The European Commission: Represents the interests of the European Union as a whole and is involved in law-making procedures.

The legally binding acts created and released by the European Union are usually adopted through the "Ordinary legislative procedure" in which the European Commission proposes the legislation in question and the European Council and the European Parliament passes the acts. [70] [71] Finally, the passed acts of the European Union need to be implemented by the individual EU-member states.

[67] Alle EU-Länder im Überblick; Generaldirektion für Kommunikation der Europäischen Kommission; March 2015; http://europa.eu/about-eu/countries/member-countries/index_de.htm

[68] Die Geschichte der Europäischen Union; Generaldirektion für Kommunikation der Europäischen Kommission ; March 2015; http://europa.eu/about-eu/eu-history/index_de.htm

[69] EU institutions and other bodies; Communication department of the European Commission; March 2015; http://europa.eu/about-eu/institutions-bodies/index_en.htm

[70] Ordinary legislative procedure; European Parliament; February 2015; http://www.europarl.europa.eu/external/appendix/legislativeprocedure/europarl_ordinarylegislativeprocedure_howitworks_en.pdf

[71] Consolidated Version of the Treaty on the Functioning of the European Union; Article 289, Official Journal C 326, 26/10/2012 P. 0001 – 0390; December 2007; http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:12012E/TXT&from=EN

7.2 Regulatory overview

All member states of the European Union are subject to the European Economic Area (EEA) law. On the European Union level, Regulation (EC) No 726/2004, and Directive 2001/83/EC are the most essential and comprehensive regulations for medicinal products within the EU that establish important overall safety relevant regulatory standards.

Regulation (EC) No 726/2004 covers the authorization and surveillance of safety of medicinal products. The purpose of the Regulation is to make the same approval conditions available to medicinal products in the entire European Union. Furthermore, the Regulation has established some regulations concerning the European Medicines Agency (EMA) with the aim, to provide groundbreaking and safe medicinal products within the shortest time frame as possible. [72] As with all EU-Regulations, Regulation (EC) No 726/2004 is a legally binding act that is valid to all EU-member states without transposing it into national law this means, it may break national law. [73] Regulation (EC) No 726/2004 requires that biological products as defined in the Annex of the Regulation be authorized by the European Commission, which means that medicinal products like biotechnology-derived products, gain marketing approval trough the Centralized Procedure as laid down in the respective Regulation. The Regulation links to Directive 2001/83/EC in regards to principles related to manufacturing, marketing and distribution and monitoring of medicinal products.

Regulation (EC) 726/2004 consists of three sections:

1. An Introduction section called the “Whereas” section;
2. The Article section which defines 90 Articles within 5 (V) Titles; and
3. The Appendix section which contains 1(I) Appendix.

The Directive 2001/83/EC acts as an important community instrument and cover a broad range of requirements for all human medicinal products. The Directive defines the essential principles and requirements for manufacturing, authorization, marketing and distribution, labeling, inspections, monitoring and postmarketing surveillance with the intention of the protection of community safety by ensuring the safety, effectiveness and quality of medicinal products. The goal of the Directive is to eliminate trade barriers through mutual recognition of state specific marketing authorizations and to harmonize applied rules and standards for medicinal products amongst each EU-member state for the marketing approval of medicinal products that are outside the scope of the Centralized Procedure (CP). To implement the Directive, each member state of the European Union must transpose the requirements of Directive 2001/83/EC into national law. [73] For example, in Germany national law is the German Drug Law (AMG). The EU-requirements may be tightened, within the transposition into national law; however, the requirements may not be reduced.

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[72] Zulassung und Überwachung von Arzneimitteln – Europäische Arzneimittel-Agentur; Zusammenfassung des Dokumentes: Verordnung (EG) Nr. 726/2004; European Union, November 2013; http://eur-lex.europa.eu/legal-content/DE/TXT/HTML/?uri=URISERV:l22149&qid=1421153176058&from=EN

[73] European Union; Regulations, Directives and other acts; European Union January 2015; http://europa.eu/european-union/eu-law/legal-acts_en

Directive 2001/83/EC consists of three sections:

1. An Introduction section called the “Whereas” section;
2. The Article section which defines 130 Articles within 14 (XIV) Titles; and
3. The Appendix section contains 3 (I-III) Appendices.

There are a number of additional Regulations and Directives that are important for biological products as well as for other human medicinal products (e.g. new chemical entities (NCE)). [74] [75] [76]

Beside of Directives and Regulations, EU-Decisions are also legally binding to the EU member states, with the difference that a Decision is only binding to a definite addressee, e.g., an EU-member state, or a specific single business. [73]

7.3 Other important documents

To complete the pharmaceutical regulatory framework, several instruments, many of them legally non-binding, but some with mandatory character are available for medicinal products in the European Union. The following list represents the most significant of them by their publisher and provides information on their legal applicability:

- The European Council or the European Parliament: legally non-binding Resolutions, Conclusions, Recommendations, Opinions; [77]
- The European Council: legally non-binding Notifications;
- The European Commission: legally non-binding Communications;
- The European Commission: legally non-binding EC-Guidelines (e.g., Notice to Applicants); and
- The European Medicines Agency (EMA): EMA-Guidelines (e.g., CHMP (Committee for Medicinal Products for Human Use) EMA scientific guidelines (e.g., quality-, safety- and efficacy guidelines)
    - In principle, EC- and EMA- guidelines are non-legally binding but they represent the position adapted by the Community and thus guidelines may be quasi-binding. [6] The quasi-binding character of a guideline may convey from the legislative basis in cases where the guideline´s purpose is to detail and specify how to execute a statutory duty (e.g., Article 106 of Directive 2001/83/EC) [6]
    - If medicinal product manufacturers or applicants of marketing authorizations decide to use alternative options to the recommended

[74] Clinical trials; European Commission, Directorate-General for Health and Food Safety ; February 2015; http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm

[75] Legal framework governing medicinal products for human use in the EU; Directorate-General for Health and Food Safety; February 2015; http://ec.europa.eu/health/human-use/legal-framework/index_en.htm

[76] EudraLex Volume 1 - Pharmaceutical Legislation Medicinal Products for Human Use; Directorate-General for Health and Food Safety; February 2015; http://ec.europa.eu/health/documents/eudralex/vol-1/index_en.htm

[73] European Union; Regulations, Directives and other acts; European Union January 2015; http://europa.eu/european-union/eu-law/legal-acts_en

[77] 3.3. The legal system of the European Union; Nicholas Moussis; February 2015; http://www.europedia.moussis.eu/books/Book_2/2/3/3/index.tkl

[6] Procedure for European Union Guidelines and related Documents within the Pharmaceutical legislative Framework; Doc. Ref. EMEA/P/24143/2004 Rev. 1 corr; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004011.pdf

guidelines they are allowed to do so provided they can rationalize their alternative approach and their deviation from the guidelines in an appropriate fashion within the application [6] [78]

- ❖ The European Directorate for the Quality of Medicines and HealthCare (EDQM): European Pharmacopoeia monographs
  - In principle and according to the "General Notices (1.1)" of the European Pharmacopoeia 8th Edition, the information in monographs represents legally binding requirements unless otherwise stated.
- ❖ Other institutions: Non-legally binding guidelines published by the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), guidelines published by the Organization for Economic Co-operation and Development (OECD) or guidelines published by the World Health Organization (WHO).

[78] Scientific guidelines; European Medicines, June 2015; Agencyhttp://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&mid=WC0b01ac05800240cb

7.4 Responsible Authorities

The European Medicines Agency

On the basis of Council Regulation (EEC) No 2309/93 the European Medicines Agency (EMA) was founded in 1993 by the EU-member states and began its work in 1995. [79] The EMA has a broad range of tasks related to the safeguarding of public health and the safety of medicinal products. The EMA takes a main role within the drug approval processes through the Centralized Procedure. Further, the EMA works closely with the European Commission by providing them scientific opinions obtained by assessing the drug dossier documents submitted by the applicants of marketing authorizations.

Other important tasks of the EMA, include but are not limited to maintaining the pharmacovigilance system of medicinal products, running the EudraVigilance database, providing scientific advice to applicants of marketing authorizations and to the EU- bodies and -member states, compiling and issuing scientific guidance documents, collaborating internationally to achieve globally harmonized requirements on drug regulation, and providing scientific evaluation of drug dossier documents within the framework of the Centralized Procedure that serves the basis for the drug approval decision made by the EU-Commission. [80] To ensure that the most current science-based recommendations are provided to the EU-Commission, the EMA is structured into seven specialized scientific committees namely:

1. The Committee for Medicinal Products for Human Use (CHMP);
2. The Pharmacovigilance Risk Assessment Committee (PRAC);
3. The Committee for Medicinal Products for Veterinary Use (CVMP);
4. The Committee for Orphan Medicinal Products (COMP);
5. The Committee on Herbal Medicinal Products (HMPC);
6. The Committee for Advanced Therapies (CAT); and
7. The Pediatric Committee (PDCO).

The European Commission

The European Commission is an important body of the European Union with a wide purpose and is comprised of one commissioner per member state. Within the Centralized Procedure, the European Commission has the final authority in the approval or denial of a marketing authorization.

[79] First general Report on the Activities of the European Agency for the Evaluation of Medicinal Products; EMEA/MB/065/95, 15 January 1996; http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2009/12/WC500016821.pdf

[80] A consistent approach to medicines regulation across the European Union, EMA/437313/2014; http://apps.who.int/medicinedocs/documents/s22187en/s22187en.pdf

The National Competent Authorities

Each EU-member state has a national competent authority (NCA) that regulates aspects related to medicinal products on the national level according to their national law. In Germany, the German Drug Law appoints the Federal Institute for Drugs and Medical Devices (BfArM) to be the German national competent authority for most medicinal products and the Paul-Ehrlich-Institute (PEI) to be the national competent authority for some other medicinal products such as advanced therapy medicinal products, vaccines and blood products. [81]

The national competent authorities of each member state fulfill many important pre- and post-authorization tasks like managing the pharmacovigilance system, conducting GxP- inspections and communicating and collaborating with the European Medicines Agency. The national competent authorities are also responsible to regulate and manage the National Procedure (NP) for medicinal products which is used when only national approval in a single member state shall be achieved. Furthermore, the national competent authorities of the EU-member states cooperate in the Mutual Recognition Procedure (MRP) and in the Decentralized Procedure (DCP) to approve medicinal products in more than one EU-member state.

Other institutions: The Heads of Medicines Agency

The Heads of Medicines Agency (HMA) is a European institution that affiliates the leading persons of the national regulatory competent authorities and the EMA, and liaises with the European Commission. One of its main functions is to facilitate the drug regulatory approval procedures, specifically the DCP and the MRP, as well as the overall regulatory system of the EU. [82]

7.5 The role of the International Council on Harmonization

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) was founded in 1990 by drug regulatory- and industry representatives from Europe, Japan and the USA with the aim to ease the processes of drug development and new drug approval by harmonization of the country specific technical requirements with regard to the safety, efficacy and quality of new medicinal products and to make these processes and regulations more effective through the harmonization of the given technical standards for registration. The ICH guidelines (e.g., on safety, efficacy, quality and multidisciplinary topics) are theoretically of a recommendatory nature, but the ICH guidelines are widely recognized by industry and regulatory authorities in the ICH and in many non-ICH regions. They also strongly influence the European and national pharmaceutical legislation as many ICH guidelines ultimately become implemented legislation. [83]

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[81] Gesetz über den Verkehr mit Arzneimitteln, AMG §77 (1) und § 77(2); Neugefasst durch Bek. v. 12.12.2005 I 3394;Zuletzt geändert durch Art. 45 G v. 29.3.2017 I 626; https://www.gesetze-im-internet.de/amg_1976/

[82] About HMA; Heads of Medicines Agencies March 2015; http://www.hma.eu/abouthma.html

[83] "Transnationalisierung der Arzneimittelregulierung: Der Einfluss der ICH-Guidelines auf das deutsche Arzneimittelzulassungsrecht"; September 2010, Volume 28, Issue 9, Engelke, K. MedR (2010) 28: 619. doi:10.1007/s00350-010-2743-9 http://link.springer.com/article/10.1007%2Fs00350-010-2743-9#page-1

7.6 Clinical Trials

Typically, clinical trials (CT) are conducted prior to a medicinal product´s marketing approval with the purpose of gathering reliable evidence on drug safety and efficacy as well as for detection and verification of new and probable side effects. As such, clinical trials represent an important pre-authorization safety standard. Clinical trials may also be used after marketing authorization is granted to follow-up on long term effects (post-authorization safety standard) and to collect clinical data for off-label usage. Clinical trial results must be provided to the authorities (e.g., EMA) in order to perform the review and evaluation of the submitted drug dossier for the marketing approval. [84]

Currently clinical trials are regulated under Directive 2001/20/EC. Under this Directive, clinical trials must be applied for and authorized by the responsible national competent authority and the country specific ethic commission. The Directive 2001/20/EC defines the term clinical trial and requires that they be conducted under good clinical trial conditions as laid down in the Commission Directive 2005/28/EC. [85] Further, Directive 2005/28/EC requires that the manufacturing of the investigational medicinal products be performed under Good Manufacturing Practice (GMP) conditions. [86]

Since Directive 2001/20/EC must be transformed into the national law of the EU-member states' some member states may tighten the requirements of this Directive and other member states may implement them into national level as they are. This can lead to country specific differences in clinical trial conditions (e.g., varying details on country specific requirements on clinical trials, delays, deadlines).

To resolve these issues, Directive 2001/20/EC will be replaced by Regulation (EU) No 536/2014 which entered into force on 16 June 2014. [87] This will lead to a harmonization of modalities on clinical trials (e.g., only one clinical trial application for multinational trials) once the regulation becomes applicable, it will ease the application process and lead to more transparency and efficiency because all clinical trial applications will be centralized with the EU-portal managed by the EMA. The most significant changes to clinical trials with Regulation (EU) No 536/2014 are summarized in **Appendix E.**

In Germany, the German Drug Law (AMG) regulates clinical trials and requires approval of clinical trials by the responsible national competent authority (e.g., the BfArM or PEI) on the basis of an Investigational Medicinal Product Dossier (IMPD). [88] In addition, an acceptance letter from the German ethics committee and a

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[84] Directive 2001/83/EC of 6 November 2001; Article 8; Article 8(i); OJL 311, 28.11.2001, p.67, Consolidated Version 16/11/2012; http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[85] Directive 2001/83/EC of 6 November 2001; Article 1; OJ L 121, 1.5.2001, p. 34, 18.07.2009; http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[86] Commission Directive 2005/28/EC of 8 April 2005; Article 10; L 91/13, 09.04.2005; http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf

[87] Clinical trials - Regulation EU No 536/2014; General information section; December 2016; https://ec.europa.eu/health/human-use/clinical-trials/regulation_en

[88] Gesetz über den Verkehr mit Arzneimitteln; §§40 – 42; Neugefasst durch Bek. v. 12.12.2005 I 3394;Zuletzt geändert durch Art. 45 G v. 29.3.2017 I 626; https://www.gesetze-im-internet.de/amg_1976/

European Clinical Trials Database (EudraCT) number is required prior to beginning a clinical trial. Via the unique EudraCT- number, the registered clinical trial and relevant study information may be found in the EudraCT- database.

Further in Germany, clinical trials must be in compliance with the provisions of Good Clinical Practice (GCP-V) in which the requirement for a EudraCT-number and information on the content of the application documents may be found. [89] The German Drug Law (AMG) defines that a planned clinical trial for biological medicinal products (e.g., mAbs) must receive an explicit written approval by the NCA prior to beginning the clinical trial. For some other medicinal products an implicit non-written approval of the NCA within 30 days is adequate unless more data are requested. [90]

As indicated above, a complicating factor which may lead to delays in initiating and conducting multinational clinical trials is the fact that under the current legislation the approvals mentioned above must be obtained from each country´s NCA accommodating a multinational clinical trial. In particular, this means that the IMPD must be submitted to each EU-country NCA accommodating the multinational clinical trial, and each NCA may request various modifications to the IMPD.

To improve this situation, the HMA in its function as Clinical Trials Facilitation Group (CTFG) worked on the implementation of harmonized modalities for multinational clinical trials and has published a voluntary procedure guidance document that provides information on the parallel review of IMP dossiers in multinational CT. [91] However, Regulation (EU) No 536/2014 will render this voluntary procedure unnecessary in the future.

For clinical trials with biological products, the EMA provides documented guidance on the specific requirements and information to be provided in documentation of clinical trials with biological investigational products. [92] A further EMA guidance document provides information to the various virus related safety requirements of IMPs. [93] Finally, the EudraLex Clinical trials guidelines and the ICH-guideline on Good Clinical Practice provide some further information on clinical trials. [94] [95]

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[89] Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen; §5, §7; Zuletzt geändert durch Art. 8 G v. 19.10.2012 I 2192; http://www.gesetze-im-internet.de/gcp-v/

[90] Gesetz über den Verkehr mit Arzneimitteln; AMG § 42(2) 7; §42(2) 4; Neugefasst durch Bek. v. 12.12.2005 I 3394;Zuletzt geändert durch Art. 45 G v. 29.3.2017 I 626; https://www.gesetze-im-internet.de/amg_1976/

[91] Guidance document for sponsors for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications; Version 4, Doc. Ref.: CTFG//VHP/2016/Rev.6; https://lakemedelsverket.se/upload/foretag/humanlakemedel/klinisk-provning/VHP sponsor version 4 final_16.06.2016.pdf

[92] Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials; EMA/CHMP/BWP/534898/2008; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/05/WC500127370.pdf

[93] Guideline on Virus Safety Evaluation of biotechnological investigational medicinal products; Doc. Ref. EMEA/CHMP/BWP/398498/2005; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003795.pdf

[94] EudraLex - Volume 10 Clinical trials guidelines; European Commission, Directorate-General for Health and Food Safety; http://ec.europa.eu/health/documents/eudralex/vol-10_en

[95] Integrated addendum to ICH E6(R1): Guideline for good clinical Practice E6(R2); http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Addendum_Step2.pdf

7.7 USA institutions and structures

The Federal Government of the United States consists of three branches:

- The Legislative branch: Known as Congress and enacts the laws;
- The Judicial branch: Consists of the courts and reviews the laws made by the Congress; and
- The Executive branch: Headed by the President, Vice-President and the Cabinet responsible for implementing the laws [96]

The US laws that have been passed by the congress of the Federal Government of the United States are assigned to certain titles and collected in the United States Code (U.S.C.) by the Office of the Law Revision Counsel. Currently the United States Code comprises 54 titles. [97] The Law related to medicinal products is found in Federal Food Drug and Cosmetic Act (FFDCA) and in the Public Health Service Act (PHSA). The United States Code does not contain any other laws or administrative rules made by state- or local administrations (state laws), regulations published by the offices of the executive branch or by one of the two other federal governmental branches listed above. [98] The latter mentioned rules and regulations may be found in the Code of Federal Regulations (CFR).

The duties and responsibilities of the executive branch are to execute and to enforce federal laws of the US including the regulations published in the CFR. To carry out these laws the executive branch uses various executive departments, 15 cabinet departments in total, and the service of independent commissions of the Federal Government as well as of executive agencies. [99] [100]

The FD&C Act is also enforced by the Code of Federal Regulations which further specifies and details the implementation of the requirements of the FD&C Act and other federal laws (e.g. the PHS Act). [101] The CFR consists of rules that have been developed by various departments and agencies of the Federal Government (e.g., the FDA) and that have been published in the Federal Register. Regulations for medicinal products issued by the FDA are enforceable administrative laws authorized by legislation enacted by the Congress and approved by the President. In order for the FDA to issue rules and regulations, the FDA must comply with the procedures stipulated by the Administrative Procedure Act (APA). [102] [101] The CFR contains 50 titles and is regulates a broad range of affairs subject to Federal laws.

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[96] How the U.S. Government Is Organized; USA.gov, U.S. government's official web portal; http://www.usa.gov/Agencies/federal.shtml#How_the_U.S._Government_Is_Organized

[97] United States Code; U.S. Government; http://uscode.house.gov/browse.xhtml

[98] United States Code; U.S. Government Publishing Office (GPO); http://www.gpo.gov/fdsys/browse/collectionUScode.action?collectionCode=USCODE

[99] A-Z Index of U.S. Government Departments and Agencies; United States Government; https://www.usa.gov/federal-agencies/a

[100] The Executive Branch; The White House (USA); https://www.whitehouse.gov/1600/executive-branch

[101] About FDA; U.S. Food and Drug Administration; http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194909.htm

[102] 5 USC PART I, Chapter 5, Subchapter V: Administrative Conference of the United States, Administrative Conference of the United States; U.S. Government; http://uscode.house.gov/view.xhtml?path=/prelim@title5/part1/chapter5/subchapter5&edition=prelim

Within these 50 CFR titles, title 21 refers to medicinal products. The Code of Federal Regulations is binding until they are revised or withdrawn and is updated annually.

7.8 Regulatory Overview

The Federal Food, Drug, and Cosmetic Act (FD&C Act) was signed into law in 1938 and is the basic regulation for medicinal products. The FD&C Act is legally binding to the FDA and Industry and is effective until modified or expired. Biological products including certain biotechnology-derived medicinal products such as medicinal products containing biotechnology-derived enzyme human Imiglucerase as an active ingredient or biological products like insulin and somatropin represent a subcategory of drugs, and therefore are regulated under the provisions of the FD&C Act. [8] [58] Despite their obvious biological nature, these products currently achieve marketing approval through the New Drug Application process which is the typical regulatory approval pathway for chemically-synthesized medicinal products that are not generics. This is substantiated by specific legal conditions of the “Patient Protection and Affordable Care Act”. [103] The generic versions of those biological products regulated under the FD&C act are called follow-on biologics. The FDA regulations (CFR) for biological medicinal products approved under the FD&C Act are established in 21 CFR Parts 200 – 499. [7]

Biological medicinal products whose licensing is not covered under the FD&C Act but under the Public Health Service Act are regulated in Title 42 of the U.S. Code. The PHS Act as federal law is also enforced by the Code of Federal Regulations. Section 351 of the PHS Act provides the legal definition for biological products and serves as the basic regulation for the licensing of these products. [11] The FDA regulations for these biological medicinal products are established in 21 CFR Parts 600-680. Examples for such biological products are drugs containing the biotechnology-derived enzyme human Galsulfase as active ingredient and medicinal products containing biotechnology-derived monoclonal antibodies as active ingredient, e.g., Infliximab. [9] [10] These biological products gain marketing approval trough the Biologics License Application. [5] The imitator versions of such biological

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[8] CEREZYME, (NDA) 020367; May 1994; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=browseByLetter.page&productLetter=C

[58] Frequently Asked Questions About Therapeutic Biological Products, Question 10: How is the manufacturing process for a biological product usually different from the process for drugs?; July 2015; http://www.fda.gov/Drugs/DevelopmentApprovalProcess/%20HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm

[103] Patient Protection and Affordable Care Act 42 USC 18001 note; Section 7002(e)(2) of the “Patient Protection and Affordable Care Act” from 03/23/2010; 03/23/2010, PUBLIC LAW 111–148; https://www.gpo.gov/fdsys/pkg/PLAW-111publ148/pdf/PLAW-111publ148.pdf

[7] Food and Drugs, Parts 200 – 499; PART 314; April 2014; https://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol5/pdf/CFR-2014-title21-vol5-chapI.pdf

[11] 42 USC § 262; April 2015; http://uscode.house.gov/view.xhtml?path=/prelim@title42/chapter6A/subchapter2/partF&edition=prelim

[9] NAGLAZYME, (BLA) 125117; May 2005; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=browseByLetter.page&productLetter=N

[10] REMICADE, (BLA) 103772; August 1998; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=browseByLetter.page&productLetter=R

[5] 21 CFR §601.2(a); April 2015; https://www.gpo.gov/fdsys/pkg/CFR-2015-title21-vol7/pdf/CFR-2015-title21-vol7-part601.pdf

products are called biosimilar products. The approval pathway of chemically-biologically combined drug products such as conjugated mAbs is also the BLA. [104]

The title 21 of the Code of Federal Regulations consists of three chapters in total. Like the other Parts, the Part 600-680 of the CFR is direct binding legislation for manufacturers of biological medicinal products within the US- market and must not be transposed or adapted any further. Pharmaceutical manufacturers that intend to market their medicinal product within the US- market must comply with requirements defined in the Code of Federal Regulation. Thus, the manufacturer must incorporate the CFR requirements into its quality system.

7.9 Other important documents

Besides the previously mentioned federal laws and CFR regulations, other regulatory documents are important to manufacturers and holders of marketing authorizations (MAH) for medicinal products. The following list represents the most significant additional regulatory documents by their publisher and provides information on their legal applicability:

- Food and Drug Administration: FDA Guidance documents e.g., CDER/ CBER Guidance for Industry published in the Federal Register
  - FDA guidance documents are not legally binding but their intention is to explain how the regulation requirements could be met. If medicinal product manufacturers or applicants of marketing authorizations decide to use alternative options to the recommended guideline documents they are allowed to do so provided the approach that is used meets the applicable laws and set of regulations [105]
  - Other legally non-binding FDA documents: Points to consider, recognized consensus standards, Inspection Guides, Letters to Industry
- The Congressional committees and Federal agencies: Congressional Committee Reports and Regulation Preambles (legally not-binding)
- The U.S. Pharmacopeial Convention (USP): The drug standards of the U.S. Pharmacopeia (USP) and of the National Formulary (NF) are monographs that are officially recognized and enforceable by the FDA. [106] Medicinal products marketed in the US must comply with the USP-NF standards.
- Other institutions: Guidelines published by the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, guidelines published by the Organization for Economic Co-operation and Development (OECD) or guidelines published by the World Health Organization (WHO).

[104] Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, Question Q II.3.; Draft Guidance, Revision 1, May 2015; http://www.fda.gov/downloads/Drugs/.../Guidances/UCM273001.pdf

[105] Code of Federal Regulations (Annual Edition 2015), 21 CFR 10.115(d)(2); April 2015; https://www.gpo.gov/fdsys/pkg/CFR-2015-title21-vol1/pdf/CFR-2015-title21-vol1.pdf

[106] About USP; The United States Pharmacopeial Convention; April 2015; http://www.usp.org/about-usp

7.10 Responsible Authorities

On the basis of the FD&C Act of 1906, the former Bureau of Chemistry became a regulatory agency in addition to its scientific functions. In July 1927, the Bureau of Chemistry changed its name to Food, Drug, and Insecticide Administration which was shortened to FDA three years later. [107] Currently, the FDA is the federal regulatory authority responsible for ensuring, protecting and enhancing the health of US consumers. The agency regulates a broad range of products such as medicinal drugs, cosmetics, biologics, food, medical devices, radiation-emitting electronic products, and veterinary products. With regard to biological medicinal products, the FDA functions cover inter alia the pre- and post-authorization phase by, for example, approving investigational human clinical studies, reviewing and evaluating drug applications, conducting manufacturer inspections, providing scientific advice and monitoring the safety of approved medicinal products. The FDA is empowered by both federal laws, FD&C Act and PHS Act, to create and enforce rules and regulations for medicinal products and to supervise this sector. [108] The FDA is part of the U.S. Department of Health and Human Services and is comprised of four divisions: [1] Medical Products and Tobacco, [2] Foods and Veterinary Medicine, [3] Global Regulatory Operations and Policy, and [4] Operations. [109]

The Office of Medical Products and Tobacco oversees four centers and one office: [1] the Center for Devices and Radiological Health (CDRH), [2] the Center for Biologics Evaluation and Research (CBER), [3] the Center for Drug Evaluation on and Research (CDER), [4] the Center for Tobacco Products and [5] the Office of Special Medical Programs. Both, CBER and CDER are responsible for the regulation of biological medicinal products. [109]

The CBER regulates classical biological products like blood, vaccines and allergenics as well as tissues, cellular and gene therapy products. [110]

Many biological products with therapeutic application which are subject to either the FD&C Act or the PHS Act are regulated by CDER since being transferred from CBER to CDER in June 2003. [111]

Specifically, this includes:

- Monoclonal antibodies intended to be used in vivo;
- Therapeutically used proteins and novel proteins;
- Products intended to modulate the immune system; and

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[107] About FDA; FDA's Origin; John P. Swann, Ph.D., June 2014; http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm124403.htm

[108] 42 USC 262: Regulation of biological products, 42 USC §262 (a)(2)(A); December 2016; http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title42-section262&num=0&edition=prelim

[109] About FDA; FDA Organization Overview; April 2015; http://www.fda.gov/downloads/AboutFDA/CentersOffices/OrganizationCharts/UCM432556.pdf

[110] About FDA; Biologics Regulated Products; June 2009; http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm123205.htm

[111] About FDA, Transfer of Therapeutic Products to the Center for Drug Evaluation and Research (CDER); April 2015; http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133463.htm#1

- Growth factors, cytokines and monoclonal antibodies intended to influence the in vivo production of hematopoietic cells.

7.11 Clinical Trials

Prior to the application for marketing approval of the biological medicinal products an investigational human clinical trial must be conducted. [112]

Before beginning such a clinical investigation, an investigational new drug application (IND) as defined in 21 CFR 312 must be filed in order to [1] allow transport and distribution of non-approved drug products through the states of the USA; [2] address any safety and efficacy issues related to the medicinal product intended to be investigated; and [3] ensure the safety and rights of the human subject's participating the clinical trial. The CFR defines when an IND is applicable, and defines exemptions for already FDA approved medicinal products. [113]

The FDA has the overall responsibility and oversight for the review, assessment, and approval of IND applications including the safety monitoring of clinical investigations under IND within the US. Similar to the EU-requirements, the review and study approval by an independent ethics committee (IEC), e. g., an Institutional Review Board (IRB) is required. [114] The IRB must be in compliance with the requirements established in 21 CFR 50 and 56 and must ensure the rights and safety of the human subjects participating in the clinical trial.

Thirty days after IND submission, the clinical investigation under the applied IND may be started if the FDA has not requested further information. [115] Similar to the European EudraCT-database, relevant information on IND clinical investigations (and other clinical trials) as well as their results may be entered into the clinical trial register database "ClinicalTrials.gov". [116] Further, the CFR requires a statement within the informed consent that sponsors are required to use the ClinicalTrials.gov database when applicable for their relevant clinical investigation. [117]

Appendix F shows the most significant differences between Regulation (EU) No 536/2014 and 21 CFR 312.

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[112] Code of Federal Regulations (Annual Edition 2014), 21 CFR 601.25 (d)(2); 21 CFR 601.25 (d)(3); http://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol7/pdf/CFR-2014-title21-vol7-part601.pdf

[113] Code of Federal Regulations (Annual Edition 2014), 21 CFR 312.2(a); 21 CFR 312.2(b); http://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol5/pdf/CFR-2014-title21-vol5-part312.pdf

[114] Code of Federal Regulations (Annual Edition 2014), 21 CFR 312.23; https://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol5/pdf/CFR-2014-title21-vol5.pdf

[115] Code of Federal Regulations (Annual Edition 2014), 21CFR§312.40(b)(1); http://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol5/pdf/CFR-2014-title21-vol5-chapI-subchapD.pdf

[116] 42 USC 282: Director of National Institutes of Health, 42 U.S.C. §282(j); May 2015; http://uscode.house.gov/view.xhtml?req=%28title:42%20section:282%20edition:prelim%29%20OR%20%28granuleid:USC-prelim-title42-section282%29&f=treesort&edition=prelim&num=0&jumpTo=true

[117] Code of Federal Regulations (Annual Edition 2014), 21 CFR§50.25(c); http://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol1/pdf/CFR-2014-title21-vol1-part50-subpartB.pdf

8 Approval procedures for medicinal products

This chapter provides information about the marketing approval procedures in the EU and USA and describes the types of scientific advice meetings that an applicant for a marketing authorization may hold with the relevant regulatory authority (EMA / FDA). Regulatory meetings are an important step within the marketing approval process.

8.1 Authorization procedures in the European Union

Medicinal products may be approved either by the national competent authority of the relevant EU-member state (national authorization), or in case of a Union approval, by the designated authority of the European Union, the EMA. Both, Article 3 of Regulation (EC) No 726/2004 and Article 6 of Directive 2001/83/EC specifically establish the authorization requirements for medicinal products prior to marketing.

The European system provides three routes for authorizing medicinal products within the EU: [1] the Centralized Procedure (CP), [2] the Decentralized Procedure (DCP) and [3] the Mutual-recognition Procedure (MRP). In addition to these three routes, the EU-member states offer National Procedures (NP) to authorize a medicinal product in only that single EU-member state for which authorization has been applied. In the following sections, the principle aspects of the CP, DCP, MRP and NP will be briefly described in their principles.

Prior to authorizing medicinal products, the EMA or the responsible national competent authority may provide scientific advice to marketing authorization applicants (MAA). An overview of that process is provided.

8.1.1 The Centralized Procedure

A marketing authorization holder that has its biotechnology-derived product approved under the Centralized Procedure (CP) is allowed to market its medicinal product in all EU-member states by holding one EU-marketing authorization. The intention of the Centralized Procedure is it to make novel, innovative and high-grade technology medicinal products to treat rare, serious, life-threatening or chronic diseases, available to all citizens of the European Union. The Centralized Procedure is legally established in Regulation (EC) No 726/2004. Regulation (EC) No 726/2004 provides information on the applicability of the Centralized Procedure and states that medicinal products listed in the Annex of the Regulation must be authorized by the European Commission through the Centralized Procedure. [118] The referenced Appendix details the medicinal products for which the Centralized Procedure is mandatory. Regarding biotechnology-derived products the Appendix states in item one:

> *"1. Medicinal products developed by means of one of the following biotechnological processes:*

[118] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, Article 3; OJ L 136, 30.4.2004, p. 1, Consolidated version 05.06.2013; http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

— 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." [118]

In Article 3(2) and 3(3) of the Regulation (EC) No 726/2004 are the types and conditions of medicinal products where the Centralized Procedure may be an alternative to other available authorization procedures. As stated there, the Centralized Procedure is optional for other cutting-edge medicinal products (new active substances) substantiating a significant innovation or such which are of interest for patients at the EU level. [118]

Prior to submission of the application, the applicant is requested to inform the EMA of the intended filing date by providing a pre-submission request form and a letter of intent to submit an application at least seven month before the submission is planned. To apply for a marketing approval under the Centralized Procedure, the applicant submits a single application dossier to the EMA that must contain all documents and data as specified in Directive 2001/83/EC Articles 8(3), 10, 10a, 10b or 11 and Annex I. [119] [120] If the applied biological or biosimilar product contains or consists of genetically modified organisms additional data requirements as defined in Directive 2001/18/EC must be addressed as well. The submitted application file of the applied medicinal product is reviewed and scientifically assessed by members of the EMA´s Committee Medicinal Products for Human Use (CHMP) for medicinal products. The tasks of the CHMP are established in Article 5 of the Regulation (EC) No 726/2004. The EMA´s Biologics Working Party (BWP) is involved in the assessment process as an expert group for evaluation of quality and safety aspects of biotechnology-derived products.

The review and assessment process consist of several steps and is managed by CHMP members of two EU-member states which function as experts for the assessment, namely the Rapporteur and the Co-Rapporteur. The assessment shall be performed within a defined timeframe of 210 days and ends with a CHMP scientific recommendation regarding the products adequacy for authorization. The scientific recommendation is then forwarded to the European Commission. If the CHMP recommendation is positive, the CHMP proposes that the applied medicinal product be approved by the European Commission. The European Commission may adopt the CHMP proposal by following the Decision Making Procedure for the Adoption of Commission Decisions and a single marketing authorization is issued to the applicant which authorizes the applicant to market the medicinal product in all EU-member states. After the medicinal product has received approval for the EU-market, a European Public Assessment Report (EPAR) is published by the EMA on the EMA website. The EPAR is an executive summary and contains an overview of the medicinal product and why it was approved by Centralized Procedure.

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[118] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, Article 3; OJ L 136, 30.4.2004, p. 1, Consolidated version 05.06.2013; http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

[119] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, Article 4; OJ L 136, 30.4.2004, p. 1, Consolidated version 05.06.2013; http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

[120] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, Article 6; OJ L 136, 30.4.2004, p. 1, Consolidated version 05.06.2013; http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

In cases where the CHMP opinion would result in not recommending the medicinal product, procedures for re-examination of CHMP opinions are available. The legal basis for re-examination of CHMP opinion in Centralized Procedures is established in Regulation (EC) No 726/2004. [121]

There are special cases within the Centralized Procedure that are not described in further detail within this dissertation; specifically, [1] the conditional marketing approval as defined in Article 14(7) of the Regulation (EC) No 726/2004, [2] the marketing approval under exceptional circumstances as defined in Article 14(8), [3] the accelerated assessment procedure as defined in Article 14(9), and [4] the marketing approval that is subject to certain conditions as defined in Article 9(4) b, c, ca, cb, cc of the mentioned Regulation.

8.1.2 The Decentralized Procedure

The legal basis for the Decentralized Procedure is established in Article 28 of Directive 2001/83/EC. The DCP is used when the medicinal product in question is not approved in any EU-member state and it is desired to obtain approval in more than one EU-member state. The DCP cannot be used when approval is required via the Centralized Procedure. The basic principle of the DCP is that the NCA(s) of the concerned member state(s) (CMS) where the medicinal product is intended to achieve the approval recognizes the [1] draft scientific assessment report to an application, [2] draft summary of product characteristics (SmPC), and [3] labeling and package insert as prepared and proposed by the NCA of the reference member state (RMS). [122] This principle is called “mutual recognition”.

The outcomes of the process are national marketing authorizations issued by the desired member states. The marketing approval is valid for five years and may be renewed after that time. [123] Through the variation system legally based on Regulation (EC) No 1234/2008 the issued marketing authorizations are maintained and their harmonization is further ensured. [124]

8.1.3 The Mutual Recognition Procedure

The legal basis of the Mutual Recognition Procedure (MRP) is established in Article 28 of Directive 2001/83/EC. The MRP is used when the medicinal product in question is already approved in an EU member state via national authorization and it is desired to obtain approval in additional EU member state(s). The MRP cannot be used when approval is required via the Centralized Procedure. When the MRP is used, the country which previously approved the medicinal product via the national authorization is automatically the reference member state (RMS). Like in the DCP,

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[121] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, Article 9(2); Article 62(1); OJ L 136, 30.4.2004, p. 1, Consolidated version 05.06.2013; http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

[122] Notice to Applicants, Procedures for Marketing Authorisation CHAPTER 2, Mutual Recognition; Revision 5, February 2007; http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap2_2007-02_en.pdf

[123] Directive 2001/83/EC of 6 November 2001, Article 24; OJ L 311, 28.11.2001, p. 67, Consolidated version 16/11/2012; http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[124] Commission Regulation (EC) No 1234/2008 of 24 November 2008, OJ L 334, 12.12.2008, p. 7, Consolidated version 04.08.2013; http://ec.europa.eu/health/files/eudralex/vol-1/reg_2008_1234_cons_2012-11-02/reg_2008_1234_cons_2012-11-02_en.pdf

the MRP relies on the principle of the mutual recognition. In this case, each involved CMS relies on the existing marketing authorization and updated scientific assessment report from the RMS.

The marketing approval is valid for five years and may be renewed after that time. [123] Through the variation system legally based on Regulation (EC) No 1234/2008, the issued marketing authorizations are maintained and their harmonization is further ensured. [124]

8.1.4 National authorization procedures

Every EU-member state has defined a national authorization procedure (NP) in its national law. Under the NP, the responsible national competent authority evaluates and determines if the applied medicinal product meets the requirements with regards to quality, efficacy and safety and therefore if it is eligible to be marketed. Typically, the NP is available for medicinal products that have not been approved in any other EU-member state as long as the medicinal product is not required to be approved via the Centralized Procedure. The NP is applicable only to market the medicinal product in question solely in the country applied for. In Germany, the national procedure is established in §§ 21-24 of the German Drug Law (AMG).

8.1.5 Approval procedures for biological and biosimilar products

The applicable authorization procedure for biological products

Biological products considered in this work are mentioned in Article 3(1) of Regulation (EC) No 726/2004 and defined in point 1 of its Annex. [26] These biological products must be authorized through the Centralized Procedure. For these products, a “full application” as described in Article 8(3) of Directive 2001/83/EC must be submitted. [125]

Applicable authorization procedures for biosimilar products

The legal basis for biosimilar product applications is established in Regulation (EC) 726/2004. [120] Application data requirements are established in Article 10(4) of Directive 2001/83/EC which provides a shortened application type for certain

[123] Directive 2001/83/EC of 6 November 2001, Article 24; OJ L 311, 28.11.2001, p. 67, Consolidated version 16/11/2012; http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[124] Commission Regulation (EC) No 1234/2008 of 24 November 2008, OJ L 334, 12.12.2008, p. 7, Consolidated version 04.08.2013; http://ec.europa.eu/health/files/eudralex/vol-1/reg_2008_1234_cons_2012-11-02/reg_2008_1234_cons_2012-11-02_en.pdf

[26] Regulation (EC) No 726/2004 Article 3(1) and Point 1 of the Annex; OJ L 136, 30.4.2004, p. 1, Consolidated version 05.06.2013; http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

[125] 1.6 What will be the legal basis for my application?; 2017; http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000167.jsp&mid=WC0b01ac0580b18196

[120] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, Article 6; OJ L 136, 30.4.2004, p. 1, Consolidated version 05.06.2013; http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

biosimilar products. [126] However, the abridged application defined in Article 10(4) of the Directive is frequently insufficient for biosimilar products due to the products' characteristics and complexity. In addition, the bibliographic applications defined in Article 10a of Directive 2001/83/EC is also frequently insufficient. [127] [128] Therefore, it may be required to submit a full application in accordance with Article 8(3) of Directive 2001/83/EC. [84]

For biosimilar products considered in this work the Centralized Procedure must be used because Article 3(1) of Regulation (EC) No 726/2004 and point 1 of the Annex of the mentioned Regulation applies. Further, a full application according to Article 8(3) of the Directive 2001/83/EC must be submitted. [127]

8.1.6 Format and content of an application dossier

Like other authorization procedures (e.g., MRP, DCP, and National Procedure) the application dossier for the Centralized Procedure must be compiled in the ICH format standard for common technical documents (CTD). The ICH CTD-standard defines the application dossier format and structure that shall be used for presenting the data and information on the quality, safety and efficacy of the applied medicinal product.

The harmonized format shall be used from all three ICH-regions, but it does not provide any information about the content (e.g., required studies and data that need to be generated) of an application dossier. The content of an application dossier may vary between countries or regions due to country or region specific requirements as well as applicants´ priorities or preferences (e.g., CTD Module 3 section 3.2.R Regional information). [129] Articles 8 and 10 of Directive 2001/83/EC, and Article 6 of Regulation (EC) No 726/2004 serve as the legal basis for the CTD-format requirement. The applicable ICH-guidelines about Quality (Q), Safety (S) and Efficacy (E) provide detailed requirements regarding dossier content information.

Since 1st of July 2003, the CTD-format is applicable to all application dossier documents submitted for marketing authorization, as well as for variations applications, extension applications, follow-up measures and renewals. [129] The CTD format consists of five modules as listed and explained below. Module 1 contains administrative and regional or country specific information as defined by the European Commission and the EU-member states regulatory authorities; thus the

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[126] Directive 2001/83/EC of 6 November 2001, Article 10(4); OJ L 311, 28.11.2001, p. 67, Consolidated version 16/11/2012; http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[127] CMDh Questions & Answers Biologicals, Question 3; Doc. Ref.: CMDh/269/2012, Rev.1, July 2016; http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Questions_Answers/CMDh_269_2012_Rev1_2016_07_clean.pdf

[128] Guide to EU Pharmaceutical Regulatory Law, Sally Shorthose, Bird & Bird LLP; 2011; ISBN 978-90-411-3658-9

[84] Directive 2001/83/EC of 6 November 2001; Article 8; Article 8(i); OJL 311, 28.11.2001, p.67, Consolidated Version 16/11/2012; http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[127] CMDh Questions & Answers Biologicals, Question 3; Doc. Ref.: CMDh/269/2012, Rev.1, July 2016; http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Questions_Answers/CMDh_269_2012_Rev1_2016_07_clean.pdf

[129] Volume 2B Notice to Applicants Medicinal products for human use, Presentation and format of the dossier Common Technical Document (CTD); May 2008; http://ec.europa.eu/health/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf

provided information may vary. The structure that is defined in Module 2-5 is used in and applicable to all ICH regions and furthermore, it is applied in certain countries that have adopted the ICH CTD-format (e.g., Swiss, Canada, and Australia).

- Module 1 is not considered as portion of the CTD. However, for electronic submissions, Module 1 is considered as full portion in the e-CTD format [130]
- Module 2: Serves as general introduction of the applied biological product and also contains summaries and overviews to quality, non-clinical and clinical information prepared by persons with relevant professional expertise
- Module 3: Contains specific data to and documentation of Chemical, Pharmaceutical and Biological information.
- Module 4: Contains detailed reports for non-clinical studies
- Module 5: Contains detailed reports for clinical studies

The Parts I to IV of Annex I of the Directive 2001/83/EC define further pre-authorization requirements to be addressed in the application dossier for medicinal products. Part I of Annex I also contains specific requirements for biological medicinal products and EudraLex Notice to Applicants Volume 2B provides further guidance for each requirement that is to be addressed in a biological medicinal products dossier. For biological and biosimilar products mandatory for the Centralized Procedure, an active substance master file (ASMF) as mentioned in Part I Module 3, Point 3.2(8), of Annex I of the Directive is not applicable. [127] For more information please refer to Appendix 5 of the EMA guidance document on ASMF. [131] Furthermore, the European Pharmacopoeia monographs 01/2005:1468 products of fermentation are not applicable. [64]

Please see **Appendix G** for a visualized explanation of the CTD format and to **Appendix H** for information on the EU-Dossier requirements for biosimilar products versus biological originator products.

8.1.7 The biosimilar product application – The time point of submission and market access

The EU has regulated the point in time when a biosimilar product application is allowed to be submitted and when a biosimilar product is allowed to be marketed.

Directive 2001/83/EC and Regulation (EC) No 726/2004 specify a data protection period for the reference product of eight years. [132] [133] According to that, a biosimilar product may be marketed after the market exclusivity of the reference

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[130] ICH eCTD Specification V 3.2., Electronic Common Technical Document Specification; July 2008; http://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf

[127] CMDh Questions & Answers Biologicals, Question 3; Doc. Ref.: CMDh/269/2012, Rev.1, July 2016; http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Questions_Answers/CMDh_269_2012_Rev1_2016_07_clean.pdf

[131] Guideline on Active Substance Master File Procedure; CHMP/QWP/227/02 Rev 3/Corr; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129994.pdf

[64] Vorlesung „Biotechnisch hergestellte Arzneimittel“, Unterlagen zum Weiterbildenden Studiengang „Master of Drug Regulatory Affairs“; Folie 43 von 183; Brake, Frau Dr. Brigitte; May 2012

[132] Directive 2001/83/EC of 6 November 2001, Article 10(1); OJ L 311, 28.11.2001, p. 67, Consolidated version 16/11/2012; http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[133] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, Article 14(11); OJL 136, 30.04.2004, p.1, Consolidated version 05.06.2013; http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

product, which is 10 years after the marketing authorization was issued, has been elapsed. This data protection period may be extended for one further year to a maximum of 11 years when new indications for the biological innovator product are obtained within the first eight years of the market exclusivity period. [133]

Article 89 of Regulation (EC) No 726/2004 defines exemptions of the periods defined in Article 14(11) and Article 90 is limiting the year of additional protection to those reference products whose initial application was submitted after 20 November 2005. [134]

8.1.8 Meeting regulatory authorities

The regulatory basis for providing scientific advice is established in Regulation (EC) No 726/2004, and in Regulation (EC) No 141/2000 for orphan medicinal products. [135] [136] Although the scientific advice is not binding for authorities or applicants, and despite of the existence of many specific scientific guidance's that are published by the EMA to advice applicants, scientific advice is an important step in obtaining the desired approval for marketing biotechnology-derived products. Therefore, advice should be requested from the authorities (e.g., EMA or NCA).

Scientific advice may be obtained in the pre-authorization phase (e.g., during development phase), or in the post-authorization phase of a biotechnology-derived product. The scientific advice may cover topics that need to be addressed within the specific periods of the lifespan of a biotechnology-derived product, especially when no product-specific guidance document is available (e.g., CHMP guidance documents).

Another important meeting which is encouraged by the EMA in view of intended marketing applications is the pre-submission meeting which should be performed about seven month before planned MAA submission. The goal is to enable the applicant to verify that the application intended for submission meets the relevant legal and regulatory requirements. [134]

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[134] European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure, 1.8. What is the period of protection for my medicinal product?; EMA/339324/2007; http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf

[135] Regulation (EC) No 726/2004 of the Parliament and of the Council of 31 March 2004, Article 56(3), Article 57(1)(n); OJ L 136, 30.4.2004, p. 1, Consolidated version 05.06.2013; http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

[136] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999, Article 6; OJ L 18, 22.1.2000, p. 1, Consolidated version 07.08.2009; http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2000_141_cons-2009-07/reg_2000_141_cons-2009-07_en.pdf

[134] European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure, 1.8. What is the period of protection for my medicinal product?; EMA/339324/2007; http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf

8.2 Approval procedures in the USA

Prior to placing a biotechnology-derived product it must be approved by the responsible competent authority, the FDA. [137]

The US-legislation provides three primary types of applications in order to request approval of medicinal products for the US-market; specifically: [1] the New Drug Application (NDA), [2] the Abbreviated New Drug Application (ANDA) and [3] the Biologics License Application (BLA). Additionally, under the PHS Act, product application procedures are provided for biosimilar or interchangeable biosimilar products. In the following sections, the NDA, the ANDA, the BLA and, as a subtype the biosimilar application will be briefly described. Prior to authorization of medicinal products, the FDA may provide options or meetings to discuss open issues with the marketing authorization applicants. An overview of that process is also provided.

8.2.1 The New Drug Application

The New Drug Application legal basis is established in the FD&C Act which is further defined by the FDA in 21 CFR 314. [7] Under the New Drug Application, all chemical and, biotechnology-derived products not covered under the PHS Act, are reviewed and approved by the FDA on the basis of the submitted full or partial application dossier. 21 CFR 314.50 provides information on the content and format of the NDA which must also contain all clinical data required by 21 CFR 312. According to the FDA review timeframes established in 21 CFR 314.100(a), CDER is requested to review and decide on the application within the 180 days "initial review cycle" after the NDA has been filed. [138] If necessary the 180 day timeframe may be extended. [139]

8.2.2 The Abbreviated New Drug Application

The Abbreviated New Drug Application legal basis is established in the FD&C Act which is further defined by the FDA in 21 CFR 314 subpart C. [7] Under the Abbreviated New Drug Application, all generic chemically-synthesized and generic biological products not covered under the PHS Act, will be reviewed and approved by the FDA´ CDER´s Office of Generic Drugs. The ANDA process is a shortened application process when compared to the NDA process in whereby data on safety and efficacy will normally not be required. In addition, generic medicinal products applied for using the ANDA process are not required to comply with the requirements defined in rules of 21 CFR Part 314. [140] 21 CFR 314.92 provides information on the suitability of the ANDA process.

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[137] 21 USC 355: New drugs; 21 USC §355(a); April 2015; http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title21-section355&num=0&edition=prelim

[7] Food and Drugs, Parts 200 - 499, PART 314; April 2014; https://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol5/pdf/CFR-2014-title21-vol5-chapI.pdf

[138] 21 CFR 314.100(a); April 2014; http://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol5/pdf/CFR-2014-title21-vol5-chapI-subchapD.pdf

[139] 21 CFR 314.60; 21 CFR 314.96; April 2014; http://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol5/pdf/CFR-2014-title21-vol5-chapI-subchapD.pdf

[140] 21 CFR Part 314.50(c), (d)(2), (4), (5), (6) and (f); April 2014; https://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol5/pdf/CFR-2014-title21-vol5-chapI.pdf

As opposed to the NDA, the ANDA does not require any preclinical and clinical data to demonstrate safety and effectiveness of the generic drug product. However, it is necessary to demonstrate that the generic drug product is bioequivalent to the original drug product through bioequivalence studies. [141]

According to the FDA´ review timeframes established in the CFR the CDER´s Office of Generic Drugs is requested to review and decide on the application within the 180 days "initial review cycle" after the NDA has been filed. [138] If necessary, the 180 day timeframe may be extended. [139]

8.2.3 The Biologics License Application

In the USA, biological products that are subject to the provisions of the Public Health Service Act become licensed through the standard Biologics License Application as defined in section 351(a) of the PHS Act. Biosimilar products that can demonstrate a high similarity to an already FDA licensed biological reference innovator product, or those that can be shown to be interchangeable with the reference product become licensed through an abbreviated pathway of the Biologics License Application as defined in section 351(k) of the PHS Act. The FDA regulations for marketing approval of these biological medicinal products are laid down in the 21 CFR Part 601.2, information to the licensing and filing procedures of the BLA are provided there. Like NDA applications, BLA applications must contain all clinical data as defined in 21 CFR 312.

The standard BLA procedure according to section 351(a) of the PHS Act is a licensure process in which the application file of a biological innovator product is submitted to the CBER or CDER department of the FDA. The application file is reviewed and scientifically assessed by the responsible FDA departments using a five phase process with the goals as described below: [142]

- Phase 1: Determination of filing the application and planning the review phase
- Phase 2: Review of the application phase:
- Phase 3: Advisory committee meeting phase
- Phase 4: Action phase
- Phase 5: Post-action phase

The FDA has a timeframe of 180 days that starts with the date the application is filed to perform the “initial review cycle” and to notify the applicant of the review outcome. [138] The review timeframe is based on the Prescription Drug User Fee Act (PDUFA) from 1992 which defines that the FDA receives user fees from companies producing

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[141] Abbreviated New Drug Application (ANDA): Generics; September 2014; http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm

[138] 21 CFR 314.100(a); April 2014; http://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol5/pdf/CFR-2014-title21-vol5-chapI-subchapD.pdf

[139] 21 CFR 314.60; 21 CFR 314.96; April 2014; http://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol5/pdf/CFR-2014-title21-vol5-chapI-subchapD.pdf

[142] Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products; April 2005; http://www.fda.gov/downloads/Drugs/.../Guidances/ucm079748.pdf

[138] 21 CFR 314.100(a); April 2014; http://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol5/pdf/CFR-2014-title21-vol5-chapI-subchapD.pdf

certain medicinal products. For biotechnology-derived products user fees are required. [143] Based on the PDUFA, certain review performance goals are defined for the FDA, and these goals are valid within the current PDFUA five year authorization period. The FDA´s review performance goals are applicable for the review of all user fee billable biotechnology-derived products. The current goals specify that the review and approval decision process shall not take more than ten month for standard review and not more than ten month for a priority review decision. [144] [145]

If the FDA denies the biologics license because the company or product does not meet the requirements established for biologics licensing the applicant may request public hearing with the FDA to hear the grounds for denial. [146] [147]

8.2.3.1 The 351(k) applications (section 351(k) of the PHS Act)

In order to create a licensure pathway for products biosimilar to or interchangeable with a FDA licensed biological reference product, the foresaid section 351(a) was amended with “subsection (k)” that allows an abbreviated approval pathway based on less product -specific preclinical and clinical data than required in a standard BLA procedure. [148] [149] Within the biosimilar application dossier, comparable analytical-, non-clinical-, and clinical study data must be submitted that demonstrates the biosimilarity of the applied biosimilar product to the chosen biological innovator products. [150] It is up to the FDA to decide, if all studies are required and to what extent. However, the five phase´ review process and the time allowed for reviewing the application documents remains the same as for a standard BLA as defined in section 351(a) of the PHS Act due to the similar complexity of the submitted documents. [151]

To speed up the review and approval process for certain innovative medicinal products, especially of those drugs intended to treat serious diseases, the FDA has created four unique approaches that shall only be listed and not discussed in further detail here; specifically: [1] the Priority Review, in which the FDA aims to achieve an

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[143] CDER Therapeutic Biologic Product; September 2015; http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM164641.pdf

[144] PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017; 2013; http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf

[145] PDUFA V: Fiscal Years 2013 – 2017; https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm

[146] 21 CFR 601.4(b); April 2016; https://www.gpo.gov/fdsys/pkg/CFR-2016-title21-vol7/pdf/CFR-2016-title21-vol7-chapI-subchapF.pdf

[147] 21 CFR 12.21(b); April 2016; https://www.gpo.gov/fdsys/pkg/CFR-2016-title21-vol1/pdf/CFR-2016-title21-vol1.pdf

[148] 42 USC 262(k); December 2016; http://uscode.house.gov/view.xhtml?path=/prelim@title42/chapter6A/subchapter2/partF/subpart1&edition=prelim

[149] FDA Webinar - FDA’s Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the US; December 2014; http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM428732.pdf

[150] Biologic License Application (BLA) Checklist; Troutman Sanders LLP; October 2015; http://www.troutmansanders.com/files/FileControl/c38042c0-a860-4179-8a50-12c1170d84fd/7483b893-e478-44a4-8fed-f49aa917d8cf/Presentation/File/Biologic%20License%20Application%20Checklist.pdf

[151] Federal register/Vol.80, No.22 / Tuesday, February 03, 2015 / Notices; http://www.gpo.gov/fdsys/pkg/FR-2015-02-03/pdf/2015-02025.pdf

application result within six month, [2] the Breakthrough Therapy, in which the FDA aims to accelerate the review of applications for medicinal products demonstrating significant improvement compared to current used therapies, [3] the Accelerated Approval, that allows the drug approval based on surrogate endpoints particularly for new medicinal products for the treatment of serious diseases; and [4] the Fast Track procedure, in which the FDA starts to relieve a successful application in the development stage of the drug intended for application specifically new medicinal products for the treatment of serious diseases are considered and to accelerate their review. [152]

8.2.4 Approval procedures for biological and biosimilar products

Applicable approval procedures for biological products

The biological medicinal products considered in this work are covered by the Public Service Health Act. They are defined by the FDA as “specified biological products”. [5] These biological products must be authorized through the Biologics License Application (BLA) as established in 42 U.S.C. 262(a).

Applicable approval procedures for biosimilar products

The biosimilar products considered in this work are covered by the Public Service Health Act, and they are biosimilar to the biological products called “specified biological products”. [5] For these biosimilar products the “section 351(k) application” applies. [150]

8.2.5 Format and content of a Biologics License Application

The ICH CTD-dossier format and structure used for Modules 2-5 is the same in all three ICH regions.

With respect to the contents of Module 1, the FDA has issued a Draft Guidance for Industry which provides further information on how to organize Biologics License Applications and gives information on the archival structure of all Modules and required quantity of copies. [153] Further, 21 CFR 601.2 details the administrative documents and specifics of a BLA.

With regard to abbreviated BLA´s for biosimilar products the United States Code defines information that such biosimilar applications must include: [154]

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[152] Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review; September 2014; http://www.fda.gov/ForPatients/Approvals/Fast/default.htm

[5] 21 CFR §601.2(a); April 2015; https://www.gpo.gov/fdsys/pkg/CFR-2015-title21-vol7/pdf/CFR-2015-title21-vol7-part601.pdf

[150] Biologic License Application (BLA) Checklist; Troutman Sanders LLP; October 2015; http://www.troutmansanders.com/files/FileControl/c38042c0-a860-4179-8a50-12c1170d84fd/7483b893-e478-44a4-8fed-f49aa917d8cf/Presentation/File/Biologic%20License%20Application%20Checklist.pdf

[153] Submitting Marketing Applications According to the ICH-CTD Format —General Considerations; Draft guidance, August 2001; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073308.pdf

[154] 42 USC §262(k)(2)(A)(i); October 2015, http://uscode.house.gov/view.xhtml?path=/prelim@title42/chapter6A/subchapter2/partF&edition=prelim

- Data derived from analytical studies, animal studies, and clinical studies that are eligible to demonstrate a high biosimilarity of the applied product to one reference product and information that are adequate to show safety, purity, and potency in the applied conditions of use; [155]
- Data that show the same mechanism of action as in the reference product is utilized;
- Evidence that the conditions of use as proposed in the labeling have been approved for the reference product;
- Data that show that the route of administration, the dosage form and the strength is the same as for the reference product;
- Data that show that the facilities involved in manufacturing, processing and packaging of the biosimilar product meet the defined applicable standards.

Please refer to **Appendix I** for information showing the content shares between a BLA dossier and an abbreviated BLA dossier.

Furthermore, it is required that a "section k" application shall contain FDA information about the safety, purity and potency of the reference product and that this information shall be publicly available. [156] Also, information demonstrating that the biosimilar product complies with the standards that allow the FDA to determine interchangeability of the biosimilar product shall be submitted. [157] The information submitted to determine interchangeability must demonstrate biosimilarity to the reference product and, in addition, demonstrates that the same clinical result as the reference product in any given patient produces can be archived and for chronically use and with regard to alternating or switching the biosimilar product with the reference product, the risk of safety and reduced efficacy shall not being greater than using the reference product without alternation or switch. [158]

Additionally, the FDA guidance document on quality considerations for biosimilarity states that a complete CMC section for the proposed biosimilar product is required as well as animal studies (including the assessment of toxicity) and clinical studies (including the assessment of immunogenicity and pharmacokinetics and/or pharmacodynamics) in addition to comparative analytical studies. [159] The FDA guidance document on scientific considerations for biosimilarity the FDA states that

[155] 42 USC §262(k)(5)(A); October 2015; http://uscode.house.gov/view.xhtml?path=/prelim@title42/chapter6A/subchapter2/partF&edition=prelim

[156] 42 USC §262(k)(2)(A)(iii); October 2015; http://uscode.house.gov/view.xhtml?path=/prelim@title42/chapter6A/subchapter2/partF/subpart1&edition=prelim

[157] 42 USC §262(k)(2)(B); October 2015; http://uscode.house.gov/view.xhtml?path=/prelim@title42/chapter6A/subchapter2/partF/subpart1&edition=prelim

[158] 42 USC §262(k)(2)(B)(4); October 2015; http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title42-section262&num=0&edition=prelim

[159] Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf

during the application review the totality of the data and information submitted in the application will be considered. [160]

8.2.6 The biosimilar product application – The time point of submission and market access

In the USA the title 42 of the United States Code defines the effective date of a biosimilar application approval. [161] The marketing approval of the biosimilar product is effective not earlier than 12 years after the date of first licensure of the reference product. Further, an application for licensure of biological products as biosimilar or interchangeable may not earlier submitted to the FDA than 4 years after the date of first licensure of the reference product. [161]

8.2.7 Meeting regulatory authorities

The regulatory basis for performing meetings between FDA and sponsors is established in various US-laws and acts, e.g., in the Prescription Drug User Fee Act of 1992 (PDUFA) for biological products and new chemical entities; in the Biosimilar User Fee Act of 2012 (BsUFA) for biosimilar products or in the Generic Drug User Fee Amendments (GDUFA) of 2012 for generics drugs. [162] Furthermore, CFR regulations detail various types of meetings like the Pre-IND meeting, the End-of Phase 1 meeting, or the End-of Phase 2 meeting.

The FDA encourages sponsors to utilize the available meeting opportunities because they play a critical role within the regulatory process. In regards to biosimilar products, the FDA expects the applicant to discuss plans for the biosimilar product development program and the intended approaches early with the FDA to ensure that there is adequate support with scientific justifications and facilitation of the biosimilar development. [163] The FDA has issued various guidance documents on the different types of meetings that are available with the purpose establishing uniform procedures in order to conduct effective, well-documented and well-managed meetings scheduled in a timely manner. [164]

Typically, three different types of meetings can be requested with the FDA for biological products: [1] Type A meeting, [2] Type B meeting and [3] Type C meeting:

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[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry, April 2015;http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

[161] 42 USC §262(k)(7)(A), 42 USC §262(k)(7)(B); October 2015; http://uscode.house.gov/view.xhtml?path=/prelim@title42/chapter6A/subchapter2/partF/subpart1&edition=prelim

[162] Industry Meeting Type; December 2014; http://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/datastandardsmanualmonographs/ucm071774.htm

[163] Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants; Guidance for Industry, November 2015; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm345649.pdf

[164] Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products; Draft guidance for Industry, March 2015, Revision 2; http://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM437431

1. Type A meeting: Used for development programs that have either become stuck and where the sponsor needs information on how to proceed, or where serious safety issues need to be discussed [164]
2. Type B meeting: Used to review the progress of the drug development [164]
3. Type C meeting: Used to discuss and clarify sponsor questions regarding site designs, development, or the medicinal product in general that may not be covered under Type A or B meetings [164]

Specifically for biosimilar products for which a biosimilar BLA according to section 351(k) PHSA applies, five different types of meetings are available for request with the FDA: [1] Biosimilar Initial Advisory Meeting (BIAM); [2] Biosimilar Product Development Type 1 Meeting (BPD); [3] Biosimilar Product Development Type 2 Meeting; [4] Biosimilar Product Development Type 3 Meeting; and [5] Biosimilar Product Development Type 4 Meeting. [163]

1. Biosimilar Initial Advisory Meeting (BIAM): Used to assess and to discuss if the biosimilar product intended for application under section 351(k) of the PHS Act is eligible for this specific licensure procedure by evaluating preliminary comparative analytical similarity data.
2. Biosimilar Product Development Type 1 Meeting (BPD): Used for biosimilar development programs that have either become stuck and where the sponsor need information on how to proceed, or where serious safety issues need to be discussed.
3. Biosimilar Product Development Type 2 Meeting (BPD): Used to discuss particular study related questions or to request specific advice on a current product development program.
4. Biosimilar Product Development Type 3 Meeting (BPD): Used to request advice for a current product development program on the basis of in-depth review of data (e.g., study reports), to receive advice on biosimilarity to the referenced biological innovator product and to gather information if and which further studies are required.
5. Biosimilar Product Development Type 4 Meeting (BPD): Used to discuss a biosimilar biological product application under section 351(k) of the PHS Act or supplements regarding its content and format.

[164] Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products; Draft guidance for Industry, March 2015, Revision 2; http://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM437431

[163] Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants; Guidance for Industry, November 2015; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm345649.pdf

9 The main legislation for biotechnology-derived products

This chapter identifies and presents the main legislation for biotechnology-derived products in the EU and the USA and significant overall safety relevant regulatory standards established therein.

9.1 Directive 2001/83/EC and Regulation (EC) No 726/2004

Directive 2001/83/EC establishes many pre-and post-authorization-, and overall safety relevant regulatory standards that apply to all medicinal products intended for human use in the EU. The most important safety relevant regulatory requirements are presented in **Appendix J**. Please note, provisions that are only applicable to specific medicinal drugs (e.g., homeopathic drugs, radio-nucleotides, etc.), or circumstances and specific provisions regarding the different MRP and DCP authorization procedures are excluded from the examination.

Regulation (EC) No 726/2004 establishes many pre-and post-authorization- as well as overall safety relevant regulatory standards that apply to all medicinal products intended for human use and that have to be authorized centrally by using the Centralized Procedure. The most important safety relevant regulatory requirements are presented in **Appendix K**.

In analyzing the information provided in **Appendix J** and **K**, the following safety relevant regulatory requirements were identified as significant and applicable to all medicinal products:

- General marketing authorization requirement prior to marketing;
- Regulatory approval pathway requirements;
- Renewal requirement;
- Manufacturing authorization requirement;
- Pharmacovigilance- and general reporting requirements (via Eudravigilance database) (e.g., Periodic Safety Update Reports (PSURs), Individual Case Safety Reports (ICSRs));
- Postmarketing monitoring and surveillance requirements; additional monitoring programs (e.g., black triangle labeling);
- Incident reporting requirements (e.g., (Suspected Unexpected) Serious Adverse Reaction ((SU)SARs));
- Labeling requirements (e.g., INN, brand name);
- Post-Authorization-Safety-Studies (PASS) or Post-Authorization-Efficacy-Studies (PAES);
- Post-authorization measures (PAMs); e.g., Follow-Up Measures (FUMs) or Specific Obligations (SOs), Appendix II condition (ANX), additional pharmacovigilance activity in the Risk-Management Plan (MEA), legally binding measure (LEG) and recommendation (REC);
- Risk management / European Risk Management Strategy (ERMS);
- Good Manufacturing Practice (GMP) and inspections (self- and announced and unannounced authority inspections);
- Summary of Product Characteristics (SmPc) and labeling / Product information;

- ❖ Falsified medicinal products / authorization or licensure requirement for wholesale, distribution, import and manufacturing;
- ❖ Variation system;
- ❖ Drug shortage pre-notification requirement (at least two month before permanent or temporary cessation occurs followed by disruption of supply the authority has to be notified).

In reviewing the information for biosimilar products that is provided in Directive 2001/83/EC and Regulation (EC) No 726/2004, it is observed that very limited legislative information is provided that specifically applies to biotechnology-derived biosimilar products e.g., determination of interchangeability, substitution of biological products with biosimilar products.

9.2 21 CFR 600 - 680

21 CFR Parts 600-680 establishes many pre-and post-authorization- as well as safety relevant regulatory standards that apply to all biotechnology-derived products under the PHS Act and intended for human use. The most significant safety relevant regulatory requirements applicable for biological products and biosimilar products that are established in relevant regulations are presented in **Appendix L**. Specific provisions only applicable to specific medicinal drugs (e.g., blood and plasma products) are exempted from the following examination.

In analyzing the information provided in **Appendix L** the following safety relevant regulatory requirements were identified as significant:

- ❖ General marketing licensure requirement prior to marketing;
- ❖ Requirements to the Regulatory approval pathway;
- ❖ Reporting of product deviations (quality issues);
- ❖ Distribution reports to FDA on half-yearly frequency;
- ❖ Pharmacovigilance system and postmarketing monitoring and surveillance (IND incidence reporting and general postmarketing drug safety issues reporting e.g., types of adverse experiences such serious (unexpected) adverse experiences; follow-up reports, medication error reports – reporting via MedWatch database; Periodic Adverse Experience Reports; Alert reports based on scientific literature; Individual Case Safety Reports (ICSRs); and "Sentinel System"; [165] [166]
- ❖ Prompt review of adverse experiences required;
- ❖ Labeling and naming requirements (e.g., official nonproprietary name (WHO/USAN, established name);
- ❖ Postmarketing safety studies requirement;
- ❖ Post-authorization measures (approved BLA annual reports);
- ❖ Risk management (Risk evaluation and Mitigiation strategies (REMS));
- ❖ Current Good Manufacturing Practice (GMP);

[165] Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines; Draft Guidance for Industry; March 2001; https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatory%20Information/Guidances/Vaccines/ucm092257.pdf

[166] The sentinel initiative; July 2010; http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM233360.pdf

- ❖ FDA Inspections with or without prior notice to verify compliance of cGMP requirements (Inspection frequency once every two years);
- ❖ Change system (comparable to the EU Variation system);
- ❖ Drug shortage pre-notification requirement (to notify FDA six month priorly) in case of discontinuance or potential interruption in the production of life-saving drugs; and
- ❖ Establishment registration and annual registration renewal.

9.3 Comparison of the overall safety relevant regulatory requirements established by legislation

The legislation from the EU and the USA is very similar in their overall safety relevant regulatory requirements and no major differences between the regions were identified. However, the FDA requires stricter reporting and processing than that required in the EU. Examples of the stricter requirements include submission of distribution reports to the FDA on a half-yearly basis, reporting of biological product deviations within 45 calendar days (quality issues) inspections performed every two years, and the requirement to perform a prompt review of adverse experiences. Furthermore, in the USA the establishment registration must be renewed annually which is not required by EU-law.

An additional difference concerns the regulation of drug shortage. While the FDA requires a notification of six month prior to a discontinuance or interruption in product manufacturing that could lead to a significant disruption of drug product availability, a notification of only two month is required within the EEA and only if the product ceases to be made available on the market either, temporarily or permanently. In an EMA reflection paper on drug supply shortages, the EMA indicates that the national competent authorities of the EU-member states and responsible institutions of the European Union are aware of the safety issue caused by drug shortage. [167]

Another difference is that while the EU requires a minimum of one qualified person to perform certain safety-related tasks (e.g., batch compliance), the FDA does not require that position. Furthermore, the EU has implemented the black triangle labeling that represents extended monitoring of new and high-risk products; a comparable instrument is not implemented in the USA.

Overall, the regulatory requirements established by EU legislation provide the manufacturers with more individual responsibility (e.g., they are responsible to watch their distributors) than the US-legislation. The main legal document for medicinal products, the Directive 2001/83/EC, need to be transposed into national law by the EU-member states while the United States Code applies without transposing into national law. The U.S.C. is interpreted and implemented by the FDA. In consequence, the EU-member states have more freedom regarding the implementation of EU legislation established in Directives. The US-legislation provides the FDA with more authority and power than the EU legislation to the EMA. For example, the FDA may order a recall of hazardous products and is allowed to

[167] Reflection paper on medicinal product supply shortages caused by manufacturing/Good Manufacturing Practice Compliance problems; EMA/590745/2012; November 2012; http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/11/WC500135113.pdf

promptly suspend biologics licenses and therefore the FDA may react more promptly and with stricter consequences for the pharmaceutical manufacturer, supplier or importer.

9.4 Pharmacovigilance – Significant activities to ensure the safety of biotechnology-derived products

Pharmacovigilance is considered an important instrument to monitor and evaluate marketed medicinal products in both, the EU and USA. In the recent past pharmacovigilance requirements were amended and the importance of market surveillance has been highlighted. Routine pharmacovigilance activities that apply to all marketing authorization holders include periodic reporting and monitoring requirements such as postmarketing safety reporting, adverse event / medication error reporting and literature monitoring. Postmarketing studies have a significant role within and after the marketing approval of biotechnology-derived products. Many of these products are intended to treat chronic diseases and therefore the duration of treatment is long term. Further, it is known that rare safety risks such as serious immune reactions induced by biotechnology-derived products may not be observed during the pre-approval clinical program. As the market share of biotechnology-derived products has increased in the past years, the focus and importance of comprehensive postmarketing- and monitoring instruments has also been increased.

Since 2007, postmarketing studies and clinical trials may be required by the FDA to further evaluate safety and efficacy of certain medicinal products after they have been approved for the US- market. This expanded authority for the FDA was implemented on September 27, 2007 when the Food and Drug Administration Amendments Act (FDAAA) was signed into law by the President and a new section 505(o) was added to section 901 of Title IX of FDAAA. Section 505(o) is relevant to all prescription drugs approved under the FD&C Act, as well as for biological products approved under the PHS Act. [168] By the amended section 505(o)(3), the FDA is now authorized to require postmarketing studies and clinical trials for applicable medicinal products. Post-approval studies or post-approval clinical trials are intended to: [1] evaluate known serious risks related to the product use; [2] evaluate any signs of serious risk related to the product use; and [3] to identify any potential unexpected serious risks when indicated on the basis of available information. [168] In the FDA guidance document about the implementation of amended Section 505(o)(3) FD&C Act, the FDA states the conditions that allow the agency the request of postmarketing studies. [169]

According to that information, postmarketing studies can be requested when:

- Scientific data lead the FDA to the decision to request a postmarketing study or clinical trial

[168] 21 USC § 505(o); March 2016; http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title21-section355&num=0&edition=prelim

[169] Postmarketing Studies and Clinical Trials -Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act; Guidance for Industry; April 2011; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm172001.pdf

- The FDA has determined that adverse reporting and pharmacovigilance system or a planned postmarketing study will not adequately address the assessment of known serious risk and signals related to product use or the identification of unexpected serious risk when such potential is indicated by data [169]

By the same section, the FDA is authorized to require periodic reports on the status of a required postmarketing study or -clinical trial. This legal requirement is further detailed in 21 CFR 601.70 that requires annual progress reports of a postmarketing study. The reporting requirements for biological products refers to both study types, postmarketing studies and clinical trials required on the basis of section 505(o) and also to agreed studies, the so called postmarketing commitments, which are required due to their approval basis according to 21 CFR 600.41. Further, section 505(o)(4) authorizes the FDA to request safety labeling changes to marketed drugs and section 505(p) requires the compliance with the approved risk evaluation and mitigation strategy (REMS).

In the EU, Directive 2001/83/EC and Regulation (EC) No. 726/2004 were amended in 2010 to extend the pharmacovigilance requirements and to include [1] the conduct of postmarketing studies; [2] the need of a risk management system and –plan; and [3] to add additional monitoring requirements. [170] [171] The amended legislation is called “pharmacovigilance legislation”, and came into effect in July 2012. That pharmacovigilance legislation was implemented through Regulation No 520/2012. [172] The pharmacovigilance legislation was complemented with the purpose to further improve the patient safety in 2012. [173] [174]

One significant requirement of the new pharmacovigilance legislation is the postmarketing instrument of post-approval studies which is established in Article 21a of the amended Directive 2001/83/EC. [175]

Post-authorization safety- and efficacy studies may be a condition of the marketing approval. Significant goals of the PASS or PAES are to detect, quantify, investigate or exclude potential safety risks such as safety after long-term treatment, and to confirm the safety or efficacy profile of a biotechnology-derived product or to evaluate the effectiveness of risk-minimization actions. [170]

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[169] Postmarketing Studies and Clinical Trials -Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act; Guidance for Industry; April 2011; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm172001.pdf

[170] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010; L 348/74 Official Journal of the European Union 31.12.2010; http://ec.europa.eu/health/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf

[171] Regulation (EU) No 1235/2010 of the European Parliament and of the Council; L 348/1 Official Journal of the European Union; http://ec.europa.eu/health/files/eudralex/vol-1/reg_2010_1235/reg_2010_1235_en.pdf

[172] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012; L 159/5 Official Journal of the European Union 20.06.2012; http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF

[173] Regulation (EU) No 1027/2012 European Parliament and the Council of 25 October 2012; L 316/38, Official Journal of the European Union, 14.11.2012; http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:316:0038:0040:EN:PDF

[174] Directive 2012/26/EU of the European Parliament and the Council of 25 October 2012; L 299/1 Official Journal of the European Union, 27.10.2012; http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:299:0001:0004:EN:PDF

[175] Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001 on the Community code relating to medicinal products for human use; OJ L 311, 28.11.2001, p. 67, Consolidated version 16/11/2012; http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

Beside the PASS and PAES requirements, the pharmacovigilance legislation also introduces the concept of additional monitoring presented by a black symbol (triangle) in the package leaflet. The black symbol is established by Article 23 of Regulation (EC) No 726/2004 and is intended for products containing novel active substances and biotechnology-derived products authorized after 1st of January 2011; and which are included in the list required by Article 23(1) of the Regulation. The black symbol represents that these products are subject to additional monitoring and makes users (e.g., patients and physicians) aware of this specific condition. A further instrument to facilitate pharmacovigilance activities is the risk management plan (RMP) which is required by Article 8(3) of Directive 2001/83/EC. Since March 2014, the summaries of RMPs are published for centrally authorized medicines on the EMA website in order to improve transparency. [176] To support the EU-pharmacovigilance legislation and the safety monitoring, the "Good Pharmacovigilance Practices" (GVP) were developed. The GVP are a huge set of documents separated into 12 single modules and will replace the pharmacovigilance guidelines established in Article 106 of Directive 2001/83/EC. [177]

Overall, appropriate activities to monitor and further confirm the safety and efficacy of biotechnology-derived products are available in both regions but their application is handled differently and on a case by case basis. [178] Possible reasons for the different handling include: [1] different scientific assessment standards evaluating the need for further safety data and risk measures; [2] different marketing experiences and available surveillance data for the product in question and/or [3] different points in time when relevant laws were enacted. For example, in the USA the postmarketing studies and postmarketing clinical trials requirement including risk evaluation and mitigation strategies (REMS) and new pharmacovigilance system requirement was added to the US law in 2007 by section 901 of the FDAAA. The European counterpart, the postmarketing safety and efficacy trials requirement including the risk management system / -plan- and new pharmacovigilance system was implemented into Directive 2001/83/EC by Directive 2010/84/EU in 2010.

[176] Risk-management plans; European Medicines March 2016; Agencyhttp://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000360.jsp&mid=WC0b01ac058067a113

[177] Good pharmacovigilance practices; September 2016; http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c

[178] FDA Approval letter of Actemra; BLA No 125276; January 2010; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125276s000Approv.pdf

10 Implementation of the regulatory requirements

Typically, the regulatory and safety relevant requirements applicable to medicinal products are highly complex and of a similar nature in both regions, the EU and USA. However, differences exist in the density and implementation of legislation. Within this chapter, the density of regulation (regulatory burden) in both regions is analyzed.

10.1 The density of regulation and the implementation of EU legislation

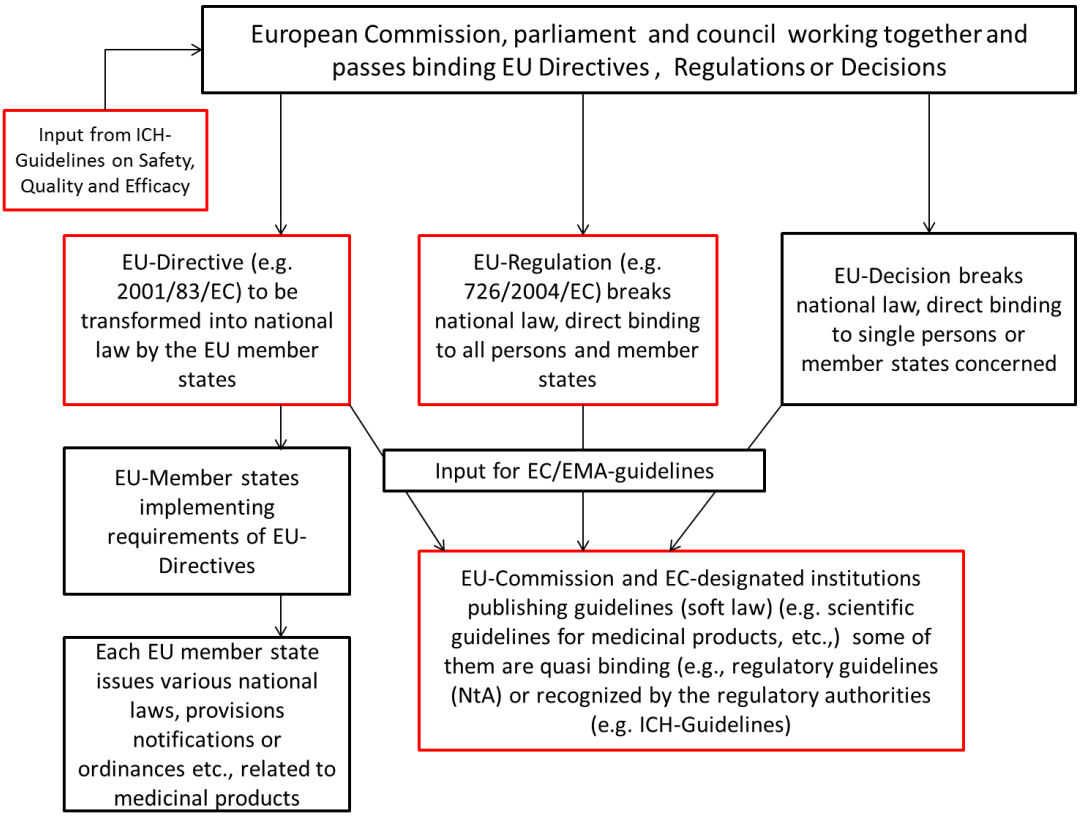
The key players within the structure and framework of the European regulatory environment are: [1] the European Commission which develops the EU legislation; [2] the EU-member states, which transform and implement indirect binding legislation into national law and, which also have the overall responsibility of securing the implementation of EU legislation at national level; [3] the EMA and, if applicable, the HMA which develop regulatory and scientific guidance documents to assist the performance of the implemented regulatory requirements; and [4] the ICH organization that develops widely recognized guidelines. Also, the requirements defined in the ICH guidelines often are incorporated into the EU legislation as well as in national laws. [83]

On the EU level, the acts proposed by the European Commission become legal through their adoption by the ordinary legislative procedure (formerly known as co-decision procedure). Once the legal act is enacted, it is the responsibility of all levels (european, federal and local) to implement the EU legislation within the the EU-member states.

Figure 3 shows the density of regulation for medicinal products, implementation structures and relations within the European Union.

[83] "Transnationalisierung der Arzneimittelregulierung: Der Einfluss der ICH-Guidelines auf das deutsche Arzneimittelzulassungsrecht"; September 2010, Volume 28, Issue 9, Engelke, K. MedR (2010) 28: 619. doi:10.1007/s00350-010-2743-9; http://link.springer.com/article/10.1007%2Fs00350-010-2743-9#page-1

Figure 3 Density of regulation, implementation structures and relations within the EU



Due the fact that within the European Union the needs of all member states must be considered and national sovereignty of each EU-member state respected and kept, it is not possible to release very detailed strict legally binding requirements EU widely and to regulate the legal requirements of all EU-member states uniformly and identically. Therefore, all EU-member states are legally obligated to transform the EU-requirements established in Directives into national law. Differences between the EU-member states in interpretation and implementation of the EU-requirements may occur which may result in legal variations and inconsistencies.

The transformation of the indirect binding requirements of any relevant Directives into national law that in turn is nationally implemented as national law, ordinances or other national types of legal documents may increase the regulatory burden and range of regulatory requirements within and between the EU-member states. Another aspect is that between the EU-member states, the implementation structure may vary leading to differences in implementation responsibilities (e.g., implementation at federal level or local level). This may also lead to differences in the density of regulation that can occur within a given EU-member state.

In order to minimize the legal inconsistencies between the EU-member states when interpreting the EU legislation, and to further explain and detail the EU legislation, the European Medicines Agency (EMA) on behalf of the European Commission is preparing and publishing “quasi binding” regulatory and scientific guideline documents with the purpose of facilitating a consistent scientific level in regards to the approval of medicinal products and defined safety standards.

In summary, the regulatory burden in the European Union is very high, comprehensive and complex in its nature due to the number of parties involved in passing, detailing and implementing EU legislation. In addition, the range of subjects covered by various legal acts is very broad with the result that the sector concerning medicinal products is well regulated.

The density of regulation for biosimilar products is basically the same as for the biologic innovator products. The requirements for biosimilar products were implemented into Directive 2001/83/EC in 2004 with Directive 2004/27/EC, and the overall requirements and safety standards defined in Directive 2001/83/EC and Regulation 726/2004/EC apply to biosimilar products as well. [179] To date, there are few overall and diverse product specific EMA scientific guidance documents available for biological and biosimilar products. The first significant overarching similar products guidance document, revised in 2014 was published in 2005. [30] So far, the European Union plays a pioneering role concerning the regulation of biosimilar products which, however, is still in an early stage. It is anticipated that more guidance documents will become available over time that address the needs of marketing authorization applicants and manufacturers of biosimilar products.

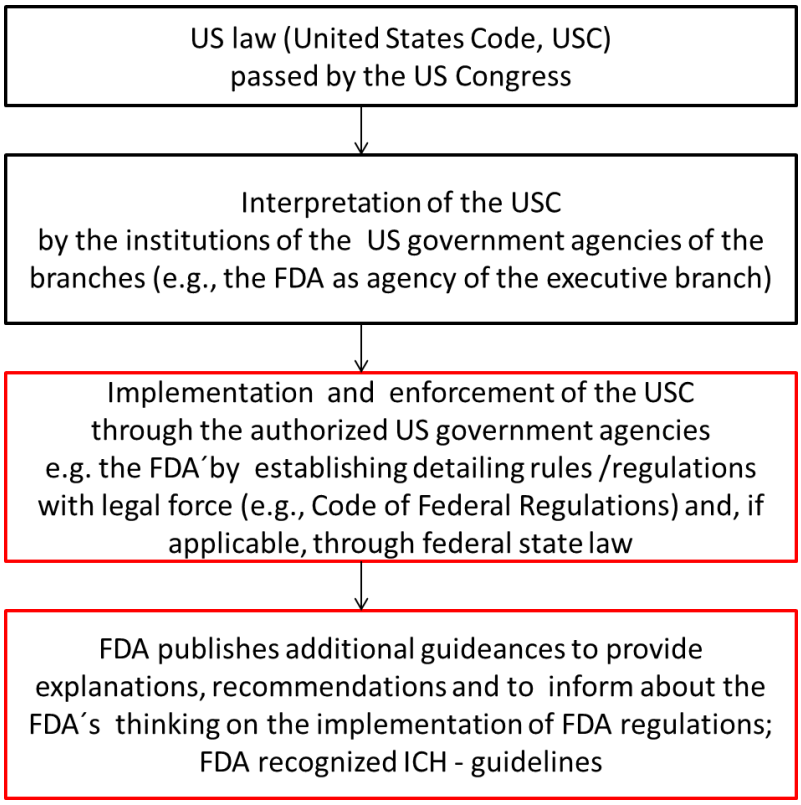
10.2 The density of regulation and the implementation of US legislation

The key players within the structure and frame of the USA regulatory environment are: [1] the US congress, that passes federal laws and statutes; and [2] the government agencies within the executive, legislative and judicial branches of the Federal government, which for medicinal products is the FDA (executive branch) which interprets, details and implements the federal laws by establishing rules and issuing relevant guidance documents. *Figure 4* shows the density of regulation and the implementation structure of the US law.

[179] Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004, L 136/34, Official Journal of the European Union, 30.04.2004; http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2004_27/dir_2004_27_en.pdf

[30] Guideline on similar biological medicinal products; CHMP/437/04 Rev 1, 23 October 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

Figure 4 Density of regulation, implementation structures and relations in USA law



Compared to the EU, the transformation of the United States law into national law is not necessary due to the different political structure. The US law passed by the US government is interpreted and further detailed in rules and regulations (e.g., Code of federal regulation) by the responsible agencies (e.g., the FDA for medicinal products). In general, states are bound to follow US law. However, there is nothing to stop any state from writing a law that contradicts US law in which case the Federal government must sue in court to overturn the state law. So, it is possible, although unlikely, that a state law contradicts the US law or regulation. Like the EU, relevant regulatory and scientific guidance documents are developed and published by the responsible agencies (e.g., the FDA for regulation of medicinal products) but these are not called “quasi binding” and are of a recommendatory nature, except for those sections where specific regulations are cited and the requirements of the regulations are reiterated.

Due to the fewer number of parties involved in implementing laws and the simpler implementation structure, the density of regulation in the USA is less intense than in the EU. The FDA´ CFR regulations are less complex than the EU legislation and national laws, but they are similar in their comprehensive nature as they cover a broad range of subjects in the sector concerning medicinal products. Therefore, this sector is regulated in the USA in a comparable intensity and manner as in the EU, but with fewer FDA guidance documents compared to that of the EMA guidance.

The density of regulation for biosimilar products is basically the same as for the innovator biological products.

To date, the FDA has published seven FDA guidance documents relevant for biosimilar products. [180] The first three guidance documents were drafted by the FDA in February 2012. It is anticipated that over time more guidance documents will become available.

[180] Biosimilars; June 2015; http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm

11 The ICH guidelines for biotechnology-derived products

The purpose of this chapter is to introduce the types of ICH guideline documents relevant for biotechnology-derived products. The ICH guideline documents address the following topics: [1] quality; [2] safety; [3] efficacy and [4] multidisciplinary items but only in the quality and safety topics, guidance specifically for biotechnology-derived products is available.

11.1 The ICH quality guideline documents

The main purpose of the quality guideline documents is to address the information and content of "Chemistry, Manufacturing and Control", also known as CMC. The CMC information has to be provided in Module 3 of the application dossier for a biotechnology-derived product. The following guideline documents for biotechnology-derived products are available:

- **ICH Q5A (R1)** *"Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin"* [181]
- **ICH Q5B** *"Analysis of the expression construct in cell lines used for production of r-DNA derived protein products"* [182]
- **ICH Q5C** *"Stability testing of biotechnological/biological products"* [183]
- **ICH Q5D** *"Derivation and characterisation of cell substrates used for production of biotechnological/biological products"* [184]
- **ICH Q5E** *"Comparability of biotechnological/biological products"* [185]
- **ICH Q6B** *"Test procedures and acceptance criteria for biotechnological / biological products"* [186]

In addition, the following guideline documents describe strategic approaches to assist in complying with the CMC:

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[181] Viral Safety Evaluation of Biotechnology Products derived from cell lines of human or animal Origin, Q5A(R1); September 1999; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5A_R1/Step4/Q5A_R1__Guideline.pdf

[182] Quality of Biotechnological Products: Analysis of the Expression construct in cells used for production of R-DNA derived Protein products, Q5B; November 1995; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5B/Step4/Q5B_Guideline.pdf

[183] Stability testing of Biotechnological / Biological Products; Q5C; November 1995; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5C/Step4/Q5C_Guideline.pdf

[184] Derivation and Characterisation of cell substrates used for production of biotechnological / biological products; Q5D; July 1997; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5D/Step4/Q5D_Guideline.pdf

[185] Comparability of biotechnological / biological products subject to changes in their manufacturing process; Q5E; November 2004; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf

[186] Specifications: Test procedures and acceptance criteria for biotechnological / biological products; Q6B; March 1999; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6B/Step4/Q6B_Guideline.pdf

- **ICH Q7** *"Good Manufacturing Practise guide for active pharmaceutical ingredients"* [187]
- **ICH Q8 (R2)** *"Pharmaceutical development"* [188]
- **ICH Q9** *"Quality Risk Management"* [189]
- **ICH Q10** *"Pharmaceutical Quality System"* [190]
- **ICH Q11** *"Development and manufacture of drug substances (chemical entities and biotechnological / biological entities)"* [191].

11.2 The ICH safety guideline documents

The main purpose of the ICH safety guideline documents is to detect and identify any potential risks related to the drug substance or –product. Currently, one guideline document is available that addresses preclinical specifics of biotechnology-derived products.

- **ICH S6 (R1)** "Preclinical safety evaluation of biotechnology-derived pharmaceuticals" [192]

[187] Good Manufacturing Practice guide for active pharmaceutical ingredients; Q7; November 2000; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf

[188] Pharmaceutical development; Q8(R)2; August 2009; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf

[189] Quality Risk Management; Q9; November 2005; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf

[190] Pharmaceutical Quality System; Q10; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf

[191] Development and Manufacturer of Drug Substances; Q11; May 2012; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11_Step_4.pdf

[192] Preclinical safety evaluation of biotechnology-derived pharmaceuticals, S6(R1); July 1997; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S6_R1/Step4/S6_R1_Guideline.pdf

12 Analysis of EMA scientific guidance documents

Within this chapter, the most significant EMA scientific guidance documents for biological innovator products applicable for mAbs as well as EMA scientific guidance documents for biosimilar products will be identified and analyzed with respect to the categories of standards impacting the safety of biotechnology-derived products. The EMA guidance documents were analyzed in order to assess how far the following categories of safety standards are addressed:

- Overall regulatory requirements
- Non-clinical considerations
- Clinical considerations.
- Quality considerations related to safety.

Various scientific EMA guidance documents for biotechnology-derived products are available on the EMA homepage. All available documents are categorized into individual sections as listed below:

- ❖ Quality
- ❖ Biologicals
- ❖ Non-clinical
- ❖ Clinical efficacy and safety
- ❖ Clinical pharmacology and pharmacokinetics
- ❖ Multidisciplinary
- ❖ ICH guidelines.

The documents in section “Biologicals” were reviewed for relevant guidance documents for biological innovator products. The documents in the “Multidisciplinary” section were reviewed for relevant guidance documents available for biosimilar products.

12.1 The EMA scientific guidance documents for biological innovator products with main focus on mAbs

In the “Biologicals” section, guidance documents are available for active substances and for finished products. The scientific guidance documents provided for active substances cover the following topics:

- ❖ Manufacture, characterization and control of the active substance
- ❖ Specifications
- ❖ Comparability and biosimilarity
- ❖ Plasma-derived medicinal products
- ❖ Plasma master file
- ❖ Vaccines
- ❖ Stability

The guidance documents in the mentioned topics are product class specific and address for example gene therapy products, allergen products. Three scientific guidance documents within the active substances guidance section were identified that may be applicable for biotechnology-derived monoclonal antibodies. These are:

1. The *"Guideline on development, production, characterisation and specifications for monoclonal antibodies and related products"* in which quality aspects for mAbs to support a marketing authorization application is discussed. [193]
2. The guideline *"Production and quality control of medicinal products derived by recombinant DNA-technology"* 3AB1a which provides information related to the data collection and submission in order to support marketing authorization applications. [194]
3. The *"Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission"* which provides advice to the data requirements for process characterization and verification in manufacturing in order to support marketing authorization applications. [195]

All three documents are intended to support marketing applications by providing advice to the data collection and compilation. This shall not be discussed in further due to the lack of relevance to the defined safety categories.

The scientific guidance documents provided for finished products cover the following topics:

- Pharmaceutical development
- Product information
- Adventitious agents safety evaluation viral safety
- Transmissible spongiform encephalopathy (TSE) (animal and human)
- Investigational medicinal products
- Genetically modified organisms (GMOs)
- Specifications

The available documents are very specific and for different product classes. Most of the guidance documents cover drug products such as plasma derived medicinal products or vaccines.

Five scientific documents were identified which may apply to biological innovator monoclonal antibody products, whereby the first three mentioned documents which are also applicable to biosimilar products.

1. The *"Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials"* [92]
2. The *"Guideline on virus safety evaluation of biotechnological investigational medicinal products"* [93]

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[193] Guideline on development, production, characterisation and specifications for monoclonal antibodies and related products; EMA/CHMP/BWP/532517/2008; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/08/WC500211640.pdf

[194] Production and Quality control of medicinal products derived by recombinant technology; 3AB1A; December 1994; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003433.pdf

[195] Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission; EMA/CHMP/BWP/187338/2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/04/WC500205447.pdf

[92] Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials; EMA/CHMP/BWP/534898/2008; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/05/WC500127370.pdf

3. The *"Note for guidance minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products"* [196]
4. The *"Guideline on the use of bovine serum in the manufacture of human biological medicinal products"* [197]
5. The *"Guideline on the use of porcine trypsin used in the manufacture of human biological medicinal products"* [198]

The guidance document in the first item discusses the requirements and information that need to be provided in the documentation of clinical trials with biological investigational products. This shall not be discussed in further due to the lack of relevance to the defined safety categories.

The guidance document in the second item addresses the viral safety of IMPs during clinical development and provides advice with respect to a clinical trial application. This shall not be discussed in further due to the lack of relevance to the defined scope and safety categories.

The guidance document in the third item addresses the issue of transmitting animal spongiform encephalitis (TSE). The guidance document provides general information on the TSE issue and provides recommendations on minimizing the risk for TSE. The document addresses neither clinical safety and non-clinical safety requirements, nor quality related safety considerations.

The guidance documents in the fourth and fifth item are applicable to biotechnology-derived products that use animal-derived materials in the manufacturing. Generally, manufacturers of recombinant proteins and mAbs should seek the use of non-animal derived materials (e.g., transgenic plant-derived trypsin, recombinant human transferrin derived from yeast or transgenic rice, etc.). The documents do not address clinical safety or non-clinical safety requirements nor quality safety relevant considerations and therefore shall not be further discussed.

Overall, no scientific guidance document was found in the "Biologicals" section that discusses one of the four defined categories of safety standards.

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[93] Guideline on Virus Safety Evaluation of biotechnological investigational medicinal products; Doc. Ref. EMEA/CHMP/BWP/398498/2005, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003795.pdf

[196] Note for guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products; EMA/410/01 rev. 3, C73/1 Official Journal of the European Union, 05.03.2011; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003700.pdf

[197] Guideline on the use of bovine serum in the manufacture of human biological medicinal products; EMA/CHMP/BWP/457920/2012 Rev1; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500143930.pdf

[198] Guideline on the use of porcine trypsin used in the manufacture of human biological medicinal products; EMA/CHMP/BWP/814397/2011; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162147.pdf

12.2 The EMA scientific guidance documents for biosimilar products with main focus on mAbs

Most of the current scientific guidance documents for biosimilar products are found in the “Multidisciplinary” section. The biosimilar guidance documents on the EMA website are categorized into the following sections:

1. Overarching biosimilar guidance documents, applicable to all biosimilar products
2. Product-specific biosimilar guidance documents
3. Other guidance documents relevant for biosimilar products and biological innovator products

Table 1 shows the applicable scientific guidance documents for biosimilar products and the categories of safety standards addressed.

Table 1 EMA biosimilar products guidance documents and categories of safety standards

Title of guidance document	Category of safety standard
Overarching biosimilar products guidance documents	
"Guideline on similar biological medicinal products" [30] Authors short title: Similar products guidance document	Overall safety-relevant regulatory requirements
"Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" [57]. Authors short title: Similar products - non clinical and clinical issues guidance document	Non-clinical safety and clinical safety requirements, Overall safety-relevant regulatory requirements
"Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues" [199] Authors short title: Similar products - quality issues guidance document	Overall safety-relevant regulatory and quality requirements
Product-specific biosimilar products guidance documents	
"Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues" [200] Authors short title: Similar products mAb guidance document	Non-clinical safety and clinical safety requirements, Overall safety-relevant regulatory requirements

Beside of the biosimilar guidance documents presented in *Table 1* several product class specific documents such as for products containing recombinant follicle-stimulating hormone or interferon beta, etc., are available for biosimilar products.

[30] Guideline on similar biological medicinal products; CHMP/437/04 Rev 1, 23 October 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

[57] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev1, 18 December 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf

[199] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1); EMA/CHMP/BWP/247713/2012, Rev.1; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167838.pdf

[200] Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues; EMA/CHMP/BMWP/403543/2010; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

In addition, the following documents are relevant for biotechnology-derived products and may address the analyzed categories of safety standards. These documents will be considered in the comparison chapter as necessary:

- *"EMA Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications"* [201]
- *"Labeling and naming (INN): WHO Guidelines on the Use of INNs for Pharmaceutical Substances (1997)"* [202]
- *"Biological Qualifier- An INN Proposal, Programme on International Nonproprietary Names (INN)"* [203]
- *"Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use"* [204]
- *"Guideline Immunogenicity assessment of biotechnology-derived therapeutic proteins"* [61]

[201] EMA Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications; EMA/940451/2011; http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125166.pdf

[202] Guidelines on the use of international nonproprietary names (INNs) for pharmaceutical substances; WHO Pharm S/NOM 1570; http://apps.who.int/iris/bitstream/10665/63779/1/WHO_PHARM_S_NOM_1570.pdf

[203] Biological Qualifier -An INN Proposal; INN Working Doc. 14.342, Rev. Final October 2015; http://www.who.int/medicines/services/inn/WHO_INN_BQ_proposal_2015.pdf?ua=1

[204] Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use; EMA/CHMP/BMWP/86289/2010; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128688.pdf

[61] Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins; EMEA/CHMP/BMWP/14327/2006 Rev1; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/10/WC500194507.pdf

13 Analysis of publicly available FDA guidance documents

Within this chapter, the most significant and publicly available FDA guidance documents for biological innovator products, especially for mAb products, and biosimilar products will be analyzed with respect to the categories of safety standards.

The FDA´s relevant publicly available guidance information can be found on the FDA website under section "Vaccines, Blood & Biologics". [205] Following guidance documents, compliance and regulatory information for "Biologics" are provided there:

- Biologics Rules (e.g., Federal Register Notices)
- Biologics Guidances
- Other Recommendations for Biologics Manufacturers (e.g., Points to consider and Memoranda)
- Biologics Procedures (FDA SOPPS (FDA Standard Operating Procedures and Policies)) for transparency purpose
- Biologics Establishment Registration (for Blood products, Human cells, tissue und cellular based products)
- Compliance Actions (Biologics)
- Biologics Post-Market Activities (e.g., Postmarketing clinical trials).

Additionally, some of the FDA guidance documents applicable for biotechnology-derived products are available in the "Drugs" section on the FDA website.

CDER publishes a list of all new and withdrawn guidance documents each year. [206] The adopted ICH-guidelines and some clinical trial guidance documents may be found in the "General" section under "Jointly issued or Agency-level guidance". [207]

13.1 The FDA guidance documents for biological innovator products with main focus on mAbs

The "General Biologics Guidance" section in "Vaccines, Blood & Biologics" contains guidance to topics like: [208]

- Administrative
- Adverse Events and Product Deviation Guidances
- Application Submissions Guidance
- Biosimilars Guidances

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[205] Guidance, Compliance & Regulatory Information (Biologics); June 2015; http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm

[206] Guidances (Drugs); April 2015; http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

[207] Biologics Guidances; July 2015; http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

[208] General Biologics Guidances; April 2015; https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/default.htm

- Clinical Guidances
- CMC and GMP Guidances
- Devices
- Generics
- Labeling and Promotion.

All guidance documents available within these topics were reviewed for applicability to mAb products and the four categories of safety standards. One guidance document was identified:

- *"Guidance for Industry for the submission of chemistry, manufacturing and controls information for a therapeutic recombinant DNA-derived product or a monoclonal antibody product for in vivo use".* [209]

This guidance document provides general information on the submission content of mAb products. It does not provide information to the defined categories of safety standards.

In addition, the section "Other recommendations for Biologics Manufacturers" provides Points to Consider (PTC) documents. [210] Here, the *"Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use"* from February, 1997 is available. [211] As the PTC´s have neither regulation nor guideline status it will not be further discussed. However, applicants of monoclonal antibody products, namely immunoglobulin's, may find some helpful information.

Two guidance documents were identified in the "Drugs" section of the FDA website: [212]

- Guidance for Industry *"Nonproprietary Naming of Biological Products".* [213]

This guidance document establishes the overall safety relevant regulatory requirements for the naming of biological products and applies to biological innovators and biosimilar products. It will be discussed in further detail in later chapters.

- Guidance for Industry: *"Immunogenicity Assessment for Therapeutic Protein Products, August 2014"* [60]

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[209] For the Submission of chemistry, manufacturing, and controls information for a therapeutic recombinant DNA-derived product or a monoclonal antibody product for in-vivo use, Guidance for Industry; August 1996; http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM173477.pdf

[210] Other Recommendations for Biologics Manufacturers; June 2010; https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/default.htm

[211] Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use, 28.02.1997; http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/UCM153182.pdf

[212] Guidances (Drugs), April 2017; https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

[213] Guidance for Industry Nonproprietary Naming of Biological Products, Guidance for Industry; January 2017; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

[60] Immunogenicity Assessment for Therapeutic Protein Products; Guidance for Industry, August 2014; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf

This guidance document applies to biological innovator and biosimilar products and informs about immune reactions to and consequences of therapeutic protein products, dependencies and relations of product- and patient-specific factors and provides risk mitigation strategies in the clinical phase of development. This guidance will be further discussed in later chapters.

The other biological products guidance documents provided in the sections “Vaccines, Blood & Biologics” and “Drugs” on the FDA´s homepage are very specific and address special topics like administrative and procedural questions, certain products, diseases and general questions.

13.2 The FDA guidance documents for biosimilar products

Both, the “Vaccines, Blood & Biologics” and the “Drugs” section provide the same publicly available FDA guidance documents for biosimilar products.

Table 2 lists the biosimilar product guidance documents and their classification into the four categories of safety standards.

Table 2 FDA biosimiliar products guidance documents and categories of safety standards

Title of guidance document	Category of safety standard
“Scientific Considerations in Demonstrating Biosimilarity to a Reference Product” [160] Authors short title: Scientific considerations guidance document	Overall safety-relevant regulatory requirements
“Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product“ [159] Authors short title: Quality considerations guidance document	Overall safety-relevant regulatory and quality requirements Non-clinical safety considerations Clinical safety considerations
“Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product” [214] Authors short title: Clinical Pharmacology	Non-clinical safety considerations Clinical safety considerations

[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

[159] Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf

[214] Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, Guidance for Industry; December 2016; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf

guidance document	
"Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 Guidance for Industry" [215] Authors short title: Biosimilar products guidance Q&A document	Overall safety-relevant regulatory requirements
"Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" [104] Authors short title: Biosimilar products guidance additional Q&A document	Overall safety-relevant regulatory requirements

In addition, the following documents are relevant for biotechnology-derived products and may address the analyzed categories of safety standards. These documents will be considered in the comparison chapter as necessary:

- *"Nonproprietary Naming of Biological Products"* [213]
- *"Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act"* [216]
- *"Labeling for Biosimilar Products"* [217]

[215] Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, April 2015, Guidance for Industry; April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

[104] Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, Question Q II.3.; Draft Guidance, Revision 1, May 2015; http://www.fda.gov/downloads/Drugs/.../Guidances/UCM273001.pdf

[213] Guidance for Industry Nonproprietary Naming of Biological Products, Guidance for Industry; January 2017; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

[216] Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act, Draft guidance, August 2014; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM407844.pdf

[217] Labeling for Biosimilar Products, Draft guidance, March 2016; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf

14 Analysis and comparison of the identified EMA and FDA guidance documents

This chapter compares and discusses the identified categories of safety standards for biosimilar products provided in the applicable EMA and FDA guidance documents.

14.1 Analysis of the overall safety relevant regulatory requirements

The following text analyzes significant overall safety relevant regulatory requirements of the USA and Europe that may influence the safety of biosimilar products and summarizes them in an overall summary.

Biological product definition and the applicable approval pathways

The Part I of Annex I of Directive 2001/83/EC and the EMA procedural advice document for biosimilar products describe a biological product as a "…*product that contains a biological substance"*, whereby the biological substance comes from a biological source. [201] Thus, diverse medicinal products such as recombinant proteins, monoclonal antibodies, products produced or extracted from human blood or plasma, or immunological and advanced therapy products are biological products. Such products require a combination of physico-chemical and biological testing to characterize the products properly and a well-controlled production process to determine product quality.

In the context of the biotechnology-derived products discussed, it is observed that monoclonal antibodies and recombinant proteins are defined as biological medicinal products. Article 3(1) of Regulation (EC) No 726/2004 establishes the mandatory scope of the Centralized Procedure requirement. According to that article, medicinal products that use the biotechnological processes described in the Annex of Regulation (EC) No 726/2004 in their development must use the Centralized Procedure as the applicable approval pathway.

The FDA describes the term biological product on their website as products that are "…*generally derived from living material--human, animal, or microorganism-- are complex in structure, and thus are usually not fully characterized".* [218] Within the US-legislation, monoclonal antibodies and recombinant protein products are

[201] EMA Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications; EMA/940451/2011; http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125166.pdf

[218] Frequently Asked Questions About Therapeutic Biological Products, Question 1. What is a biological product?; July 2015; http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm

covered by the Public Service Health Act and are defined by the FDA regulations "*specified biological products".* [27]

In the context of the biotechnology-derived products discussed, monoclonal antibodies and recombinant proteins are considered as *"specified biological products"* in the US regulation. This is in contrast to the EU definition which considers these products as *"biological medicinal products".*

Compared to the EU approval pathway, the Biologics License Application established in 21 CFR § 601.2(a) is the applicable licensure pathway. Of interest is the exclusion requirement in 21 CFR § 601.2(c)(1) which applies only to the *"specified biological products".* The exclusion requirement establishes the non-applicability of the sections §§ 600.10(b) and (c), 600.11, 600.12, 600.13, 610.53, and 610.62 of this chapter. [219]

Biosimilarity

Within the EU region, the EMA similar products guidance document considers the term *"biosimilar"* for biological products that contain "…*a version of the active substance"* of an EU authorized biological innovator product (reference product). [30] Similiarity to the authorized biological innovator product shall be demonstrated through extensive comparability testing *"…in terms of quality characteristics, biological activity, safety and efficacy".* [30]

In the US regulations, Section 351(i)(2) of the PHS Act provides the regulatory basis and legal definition of the term *"biosimilar"* in reference to a biological product. Following that definition, the term *"biosimilar"* refers to a biological product that is "…*highly similar to the reference product notwithstanding minor differences in clinically inactive components;"* and further clarifies the term "highly similar" by stating, that there are "…*no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."* [32]

Both regions, the EU and USA, refer to a reference product and require demonstration of a similar product safety.

[27] 21 CFR §601.2(a); April 2014; http://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol7/pdf/CFR-2014-title21-vol7-part601.pdf

[219] 21 CFR § 601.2(c)(1), April 2016; https://www.gpo.gov/fdsys/pkg/CFR-2016-title21-vol7/pdf/CFR-2016-title21-vol7.pdf

[30] Guideline on similar biological medicinal products; CHMP/437/04 Rev 1, 23 October 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

[32] 42 USC §262 (i)(1), 42 USC §262 (i)(2)(A),(B); April 2015; http://uscode.house.gov/view.xhtml?req=%28title:42%20section:262%20edition:prelim%29%20OR%20%28granuleid:USC-prelim-title42-section262%29&f=treesort&edition=prelim&num=0&jumpTo=true

Reference product

Within the EU, the reference product must be a biological innovator product, authorized in the EEA by a Member State or by the EU-Commission on the basis of a full dossier as established in Article 8 of Directive 2001/83. [84] [201] It is required to use one, and only one single reference product throughout the comparability program. [30] However, the comparison of the biosimilar product with a biological innovator product not authorized in the EEA may be acceptable for certain clinical studies and for in-vivo non-clinical studies provided, that the non-EEA authorized reference product was approved by a regulatory authority using a similar level of scientific and regulatory standards as the EMA applies. As detailed in the EMA´s similar products guidance and the EMA advice document for users of the Centralized Procedure, the applicant must present comparative bridging data, e.g., structural and functional data from analytical studies, data from clinical PK and/or PD bridging studies. [201] These data must show that the non-EEA authorized biological innovator product represents an EEA-authorized biological comparator product and the proposed biosimilar product. [30] [201] Although the final determination of the adequacy of bridging data will be made during application review, the EMA recommends discussing such an approach, if intended, with them upfront. [201]

Like the EU legislation, PHS Act requires that the reference product, against which a biosimilar product is evaluated, shall be a single biological innovator product which is FDA licensed under subsection 351(a) PHS. [220] [221] Similar to the EU regulatory requirements, the FDA scientific considerations guidance document, and the biosimilar products guidance Q&A document allow the use of certain comparative animal or clinical data generated with a non-U.S.-licensed product to support a biosimilarity demonstration. [160] [215] However, the following additional requirements are also specified "…*at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study, [...] must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product…."* [215] If such study is not needed, this shall be scientifically justified.

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[84] Directive 2001/83/EC of 6 November 2001; Article 8; Article 8(i); OJL 311, 28.11.2001, p.67, Consolidated Version 16/11/2012; http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[201] EMA Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications; EMA/940451/2011; http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125166.pdf

[30] Guideline on similar biological medicinal products; CHMP/437/04 Rev 1, 23 October 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

[220] 42 USC § 262(i)(4); April 2015; April 2015; http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title42-section262&num=0&edition=prelim

[221] Information for Consumers (Biosimilars), August 2015; http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm

[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

[215] Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, April 2015, Guidance for Industry; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

With regard to suitable bridging data, it is required that this information can *"…scientifically justify the relevance of these comparative data to an assessment of biosimilarity…"* and further, that this data shall establish an appropriate brigde to the U.S.-licensed reference product. [215] Such bridging data shall include "…*data from analytical studies […] that directly compare all three products […], and is likely to also include bridging clinical PK and/or PD study data for all three products…."*[215]

But in regard to product interchangeability, the biosimilar products guidance Q&A document states that it is *"…unlikely that clinical comparisons with a non-U.S.-licensed product would be an adequate basis to support the additional criteria required for a determination of interchangeability with the U.S.-licensed reference product."*[215]

Like the EMA, the FDA requires the non-US licensed comparator product to have been licensed under similar regulatory and scientific standards as US regulatory standards. The FDA´ biosimilar products guidance Q&A document provides very detailed information on the use of a non-licensed comparator product and necessary bridging data. The FDA encourages sponsors to discuss such an approach during the development program. [160]

Interchangeability

The PHS Act defines the additional standard of "interchangeability" for a biosimilar product. Interchangeability refers to the medical practice of changing one biotechnology-derived medicinal product for another biotechnology-derived product that is equal, in a given clinical setting on the initiative or with the agreement of the prescriber. A centralized approach is applied to determine the interchangeability of such product with the FDA. [222]

To meet that standard, an interchangeable biosimilar product is expected to generate the same clinical outcome as the reference product in any given patient. For a product that is administered more than once, it is required that the safety risk is not increased nor the efficacy is reduced due to alternating or switching when compared to the repeated use of the reference product without alternating or switching. This means that the interchangeable biosimilar product can be substituted for the reference product without any additional or higher risks. [223]

[215] Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, April 2015, Guidance for Industry; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

[222] 42 USC §262(k)(3); April 2015, http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title42-section262&num=0&edition=prelim

[223] 42 USC §262(i)(3), April 2015; http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title42-section262&num=0&edition=prelim

42 U.S.C §262(k)(2)(B) defines the requirement of providing information to the FDA that demonstrates that the biosimilar product complies with the standards in order to allow the FDA to determine the interchangeability of a biosimilar product. [224]

The FDA´ biosimilar products guidance Q&A document specifies the requirements and further explains the term interchangeability. [215] According to the information provided, the applicant must demonstrate product biosimilarity and, in addition, demonstrate that the proposed interchangeable biosimilar product "…*can be expected to produce the same clinical result as the reference product in any given patient…"* and further, it is to demonstrate that *"…the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch…"* if the interchangeable product is administered multiple times to an individual. [215]

Once a biosimilar product has received interchangeability status, it may automatically be substituted for the original biological innovator product by the retailing pharmacist, assuming that the applicable US state provision has enforced the US federal law on biosimilar automatic substitution. [223] [225] Automatic substitution refers to the practice whereby a pharmacist is obliged to dispense one medicine instead of another equivalent and interchangeable medicine due to national or local requirements. Following sample demonstrates different requirements to the automatic substitution in the different US-states. In one state, the physician can deny automatic substitution by adding information to the prescription, e.g., in California the information "brand medically necessary" or "dispense as written". Alternatively, in Arizona the physician must be notified about a substitution. In other states the pharmacy just switches the original biological product against the interchangeable biosimilar product without informing the physician e.g., in Florida provided the biosimilar product has been determined interchangeable by the FDA. [226] The differences in the approach on automatic substitution requirements is justified by various factors like traceability and identification issues of the substitutes, pharmacovigilance hurdles, safety / efficacy aspects (e.g., Immunogenicity concerns) or patients-associations.

Unlike the US regulations, the possibility of interchangeability is not reviewed during the approval review process with the European regulatory authority (EMA) and the topic is also not discussed by the EMA due to the lack of authority regarding this question. The EMA states in their procedural advice document for biosimilar

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[224] 42 USC §262(k)(2)(B), April 2015; http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title42-section262&num=0&edition=prelim

[215] Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, April 2015, Guidance for Industry; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

[223] 42 USC §262(i)(3), April 2015; http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title42-section262&num=0&edition=prelim

[225] US state legislation on biosimilars substitution; Generics and Biosimilars Initiative Journal (GaBI Journal), 2013; 2(3):155-6; DOI: 10.5639/gabij.2013.0203.040; http://gabi-journal.net/us-state-legislation-on-biosimilars-substitution.html

[226] **S**tate Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars, September 2016; http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx

products, those decisions regarding product interchangeability and substitution are in the responsibility of the national competent authorities. [201] Thus, the criteria and decision on product interchangeability and automatic substitution rest with the EU-member states. While some EU-member states (e.g., France) allow a restricted biosimilar substitution, many EU-member states (e.g., Norway, Spain) have introduced laws against it. [227] The decentralized approach on interchangeability and automatic substitution is justified by various factors like traceability and identification issues of the substitutes, pharmacovigilance hurdles and safety / efficacy aspects (e.g., Immunogenicity concerns) and is based on the missing EU legislation addressing the interchangeability topic.

Exclusivity and data protection periods

A similar biological product application may be submitted after the exclusivity periods established by the BPCI Act and explained in the "Background" information of the FDA´ biosimilar products guidance Q&A document. [215] According to that guidance information, there is a 12-year exclusivity period for the reference product starting from the date of first licensure. During this period the *"…approval of a 351(k) application referencing that product may not be made effective.:"* [161]

Further, a 4-year exclusivity period is defined from "…*the date of first licensure of the reference product, during which a 351(k) application referencing that product may not be submitted…"*[161]

Also, for the first biosimilar product determined to be interchangeable with the reference product for any condition of use, an exclusivity period is established by the BPCI Act. [215] During this period "…*a second or subsequent biological product may not be determined interchangeable with that reference product…"* and typically, the duration of this period takes one year. [228]

Within the EEA, a similar biological product application may be submitted through the Centralized Procedure after the applicable period of data exclusivity and protection period ends which depends on the approval procedure that was used for the reference product. The EMA procedural advice guidance document describes a 10-year or eight year protection period for a centrally authorized reference product and a *"…6/10-year protection period, depending on the Member State which has granted the marketing authorisation or 8-year protection period,…"* for a nationally

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[201] EMA Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications; EMA/940451/2011; http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125166.pdf

[227] Legislations on biosimilar interchangeability in the US and EU – developments far from visibility, June 2015; http://www.gabionline.net/Sponsored-Articles/Legislations-on-biosimilar-interchangeability-in-the-US-and-EU-developments-far-from-visibility

[215] Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, April 2015, Guidance for Industry; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

[161] 42 USC §262(k)(7)(A), 42 USC §262(k)(7)(B); October 2015; http://uscode.house.gov/view.xhtml?path=/prelim@title42/chapter6A/subchapter2/partF/subpart1&edition=prelim

[228] 42 USC 262(k)(6), July 2016; http://uscode.house.gov/view.xhtml?req=(title:42%20section:262%20edition:prelim)%20OR%20(granuleid:USC-prelim-title42-section262)&f=treesort&edition=prelim&num=0&jumpTo=true

authorized reference product. [201] If the reference product is also authorized in member states with a 10 year protection period, then this period must have been expired before the biosimilar product application can be processed via the Centralized Procedure. [201] In the case, the marketing authorization holder applies and receives authorization for new indications during the first eight years of those 10 years and these indications show a significant clinical benefit in comparison with existing therapies, then the 10-year protection period is extended to 11 years maximum. Similarly to the USA, the protection period starts with the date of notification of the marketing authorization decision to the applicant. Since the concept of interchangeability is not defined in the EU regulations, no exclusivity period for interchangeable biosimilar products is provided in the EU.

While the protection period is typically 10 years in the EU with a maximum of 11 years, the product exclusivity period for the referenced innovator is 12 years in the USA. After expiry of the relevant periods a biosimilar product can be placed on the market when approval has been granted.

Drug Master File

In both, the USA and the EEA, the Drug Master File (DMF) document is not accepted for the authorization application of a biosimilar product. [131] [159].

Naming and labeling

The international nonproprietary name (INN) for an active substance must be requested from the World Health Organization (WHO) by the innovator of the active substance or the marketing authorization applicant. The WHO, then designates a generally accessible and non-protected INN. National and / or international legislation requires the use of INNs in many uses like labeling, advertising and promotion, literature, etc. The INN is intended to clearly identify active substances with uniform designations in order to promote drug safety and pharmacovigilance systems at an international level. [229] The US naming system, called United States Adopted Names (USAN) is the American counterpart of the INN system and almost always adopts the INN so that both systems very similar. Due to the general product complexity of and structural differences, even in highly similar biotechnology-derived products, the INN system may be challenging for biosimilar and interchangeable products.

42 USC §262(a)(1)(B)(i) requires a proper name as defined in 21 CFR 600.3(k) for biological products. The use of the INN system and the USAN system seems inappropriate for biosimilar products for the US- market and its specific requirements

[201] EMA Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications; EMA/940451/2011; http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125166.pdf

[131] Guideline on Active Substance Master File Procedure, CHMP/QWP/227/02 Rev 3/Corr; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129994.pdf

[159] Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; Guidance for Industry; April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf

[229] Guidance on INN; http://www.who.int/medicines/services/inn/innguidance/en/

as it contains some disadvantages, such as lack of consistency, predictability, and uniqueness (e.g., the name “interferon beta-1α” applies to several products in the US- market). [230] In order to ensure a well-functioning pharmacovigilance and tracking system, a clear identification of all biological products and differentiation between interchangeable and non-interchangeable biosimilar products is necessary to avoid unintentional substitution; therefore shared nonproprietary names are not appropriate. [230]

To improve the naming situation, the FDA distributed a draft guidance document for the nonproprietary naming of biological products in August 2015, which was finalized in early 2017. [213] In that document, the FDA proposes the use of a FDA designated nonproprietary name. This FDA designated name is a so called proper name consisting of a shared core name (which again is the component shared among a biological innovator product and the related biological and biosimilar or interchangeable products as part of the proper names of those products) plus a FDA-designed product unique suffix. This suffix consists of four letters which enable to distinguish between biological innovator products, biosimilar products and related biological products (e.g., innovator product name replicamab-cznm; biosimilar product name replicamab-hixf) licensed under the PHS Act. [213] For biological innovator products, the FDA adopted core name for the active substance which was designated by the USAN Council is intended to be used when available. For biosimilar, interchangeable and related biological products, the core name will be the same as the core name identified in the proper name of the applicable previously FDA licensed biological innovator product. The positioning of the identifier as a suffix shall ease grouping in electronic databases and promote identification and localization of biological products with the same core name.

Initially for interchangeable biosimilar products, the FDA was gathering public input on two options: [1] the proper name should also include an individual suffix; or [2] the proper name should share the same suffix as its reference product (e.g., the proper name of the reference product as well as the interchangeable biosimilar product could be replicamab-cznm). Now, in the finalized guidance document, the FDA considers applying a similar naming policy as biosimilar products have and will use the same approach of that of a core name and a suffix included in the proper name, but the FDA is still searching for the appropriate suffix format for interchangeable products. [213]

With regard to the prescription information, on the FDA website, the FDA informs healthcare professionals about prescription requirements for interchangeable and non-interchangeable biosimilar products. According to that information, there is no difference in prescribing biosimilar and / or interchangeable products and any other medicinal products, which means, that either the proprietary name or the nonproprietary name may be documented on the prescription. It is Important to note that due to the fact that a biosimilar might be approved for fewer indications and conditions of use than its reference product is licensed, the healthcare professional

[230] “Nomenclature of New Biosimilars Will Be Highly Controversial”, Ronald A. Rader; June 2011; https://www.ftc.gov/system/files/documents/public_comments/2014/02/00013-88587.pdf

[213] Guidance for Industry Nonproprietary Naming of Biological Products, Guidance for Industry; January 2017; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

must always check the product labeling (prescribing information) to avoid prescription errors. [231] In principle, interchangeable biosimilar products may be automatically substituted at the pharmacy without the co-determination of a healthcare professional, if not otherwise regulated by state law.

In order to assist applicants in addressing labeling specifics of biosimilar products for submission purpose, the FDA has issued recommendations to industry in a labeling guidance document which provides information to the content of the prescribing information (package insert). The guidance document recommends, among other things, a “Biosimilarity Statement” in the “Highlights of Prescribing Information” section which provides information to the relationship of the biosimilar product to its reference product. [217] However, the labeling of interchangeable biological products is not considered in this guidance.

Within the EEA, according to Article 1(21) of Directive 2001/83/EC medicinal products to be authorized in the EEA shall provide a common name. Ideally the name shall be the INN, but if such does not exist, the usual common name may be used. For biosimilar products, the applicant may either apply the INN used for the reference biological product or may request a new INN from the WHO if no suitable INN is available. [201]

Similar to the FDA and upon requests of international drug regulatory authorities in the past years, the WHO has realized that the naming situation for biological products needs to be improved to ensure clear product identification and traceability. Thus, the WHO started examining different solutions in 2012 and issued a five page final document for INN proposal of biological products in October 2015. [203] The INN proposal document envisages a biological qualifier (BQ) code that is specifically assigned by the WHO to all biotechnology-derived substances having or eligible to have INNs. The BQ is intended to improve the prescription and dispensing of biological substances to aid in pharmacovigilance and to support the overall transfer of prescriptions. It is planned to apply the mechanism retrospectively. The biological qualifier is a four letter random alphabetic code that will be added as unique identification code to the INN. It is used in conjunction with the INN but will remain independent from the INN. [203] The BQ scheme may be used voluntarily by any regulatory authority and would be recognized worldwide. The INN proposal document does not explain if and how the BQ is eligible to distinguish between biological and biosimilar products and between substitutable (interchangeable) and non-substitutable (non-interchangeable) biosimilar products in order to avoid unintentional substitution.

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[231] Information for Healthcare Professionals (Biosimilars), August 2015; http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241719.htm

[217] Labeling for Biosimilar Products, Draft guidance, March 2016; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf

[201] EMA Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications; EMA/940451/2011; http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125166.pdf

[203] Biological Qualifier -An INN Proposal; INN Working Doc. 14.342, Rev. Final October 2015; http://www.who.int/medicines/services/inn/WHO_INN_BQ_proposal_2015.pdf?ua=1

With regard to the prescription of biological innovator products, the requirement defined in Article 1(21) of Directive 2001/83/EC which is the INN requirement, is slightly modified by the Directive 2012/52/EU in order to implement the requirements of Directive 2011/24/EU. [232] The modification is described in the Annex of Directive 2012/52/EU and defines that a prescribed biological product shall be identified, amongst other information, with the brand name instead of the INN on the medical prescription. [233] The identification by brand name is not required for other medicinal products. However, no information related to biosimilar product is provided in the mentioned Directive. There is no EMA guidance document comparable to the FDA´s labeling guidance for biosimilar products available in the EU.

While the INN system works well for classic generic drugs (e.g., chemically-synthesized substances), it does not work well for complex biological, biosimilar products and interchangeable products due to lacking a clear identification and traceability which may negatively impact drug safety and pharmacovigilance. [230] However, to this date, biosimilar products are marketed under the same INN as the innovator biological product in the EEA.

Container Closure System

According to the FDA biosimilar products guidance Q&A document, the FDA may accept slight deviations in the design of a delivery device, (e.g., the use of an auto-injector device instead of a vial), or container closure system between the compared products. [215] This is accepted by the FDA when the following conditions are met: [1] it must be demonstrated that the varying delivery device or container closure system is compatible with the final product formulation, and this may include performance testing and a human factors study and other studies such as extractable/leachable studies and stability studies; [2] the design difference may not result in clinically meaningful difference with respect to the products safety, purity, and potency; and [3] the design difference may not result in a different route of administration or dosage form or condition of use for which the reference product is not approved. [215] The FDA also accepts a different formulation of the biosimiliar product than the reference product owns. Here, the applicant must demonstrate that the proposed biosimilar product is highly similar to the reference product and no clinically meaningful differences with respect to the products safety, purity, and potency exist. If the proposed product is a proposed interchangeable product, the FDA regulations are stricter. In such cases, the FDA also reviews if the differences between the biosimilar and the reference product influence any critical design attributes, product

[232] Directive 2011/24/EU, Article 11(2); L88/45, Official Journal of the European Union, 04.04.2011 http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011L0024&from=DE

[233] Commission Implementing Directive 2012/52/EU, Annex of Directive 2012/52/EU, L 356/68, Official Journal of the European Union, 22.12.2012; http://ec.europa.eu/health/cross_border_care/docs/impl_directive_presciptions_2012_en.pdf

[230] “Nomenclature of New Biosimilars Will Be Highly Controversial”, Ronald A. Rader; June 2011; https://www.ftc.gov/system/files/documents/public_comments/2014/02/00013-88587.pdf

[215] Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, April 2015, Guidance for Industry; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

performance, etc., or require additional use instructions. Thus, the FDA may require additional performance data for the delivery device or container closure system. [215]

The FDA guidance document about immunogenicity assessment for protein products should be considered specifically for monoclonal antibodies and other complex protein therapeutic products. [60] It recommends maintaining detailed raw material data of the container closure system and further, to perform an extensive extractables and leachables laboratory assessment in order to evaluate the attributes of the system and possible interactions that could lead to degradation of the product structures. [60] It should be noted that the tests described in the United States Pharmacopeia *"Elastomeric Closures for Injections"* do not address the specifics of storage containers used for products like monoclonal antibodies under real-time conditions. Therefore, additional testing for leachables under stress- and under real time storage conditions should be performed for each product and its storage container. [60]

Similar to the accommodation in the FDA Q&A guidance document the EMA´s similar products- quality guidance document also provides the possibility of using a different container or closure system than the reference product uses; provided that its potential impact on the biosimilar´s product safety and efficacy is appropriately justified. [199] In contrast to the FDA guidance document the EMA document does not further detail the topic or requires any additional data. For any used active substance formulation of the biosimilar product, the applicant shall demonstrate their eligibility regarding stability, compatibility, activity, strength and integrity. The applicant shall consider the common requirements that apply for testing a formulation.

Pediatric assessment

US legislation defines that a biosimilar product not holding the interchangeable status is considered as a "new active ingredient" in terms of the Pediatric Research Equity Act (PREA). [234] Therefore, a pediatric assessment is required unless waived or deferred. [235] Biosimilar products determined to be interchangeable with its reference product are excluded from the pediatric assessment requirement, as such products are not considered to have a "new active ingredient". However, PREA requirements must be fulfilled when an applicant applies for licensure without

[215] Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, April 2015, Guidance for Industry; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

[60] Immunogenicity Assessment for Therapeutic Protein Products; Guidance for Industry, August 2014; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf

[199] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1); EMA/CHMP/BWP/247713/2012, Rev.1; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167838.pdf

[234] 21 USC §355c (a)(1); 21 USC §355c (l)(1),(2), April 2015; http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title21-section355c&num=0&edition=prelim

[235] 21 USC §355c(a)(3),(4), April 2015; http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title21-section355c&num=0&edition=prelim

providing interchangeability status even if it intends to amplify the licensure at a later date with the interchangeability status. [215]

According to the current EU pediatric legislation Regulation (EC) No 1901/2006, the requirement to submit a pediatric investigation plan does not apply, to biosimilar products because the approval basis for such products is the demonstration of comparability. [236] This is in contrast to the US legislation requiring a pediatric assessment for biosimilar products without interchangeability status, and this is despite the fact that biosimilar products in EU are considered as "new active substance". [237]

Pharmacovigilance and post-approval safety monitoring considerations

The FDA considers a robust post-approval safety monitoring program and risk evaluation and mitigation strategies as defined under the Federal Food, Drug, and Cosmetic Act as crucial to ensure the safety and efficacy of biotechnology-derived products. For this purpose, it is important to monitor the safety or effectiveness related to the reference product and its product class, the proposed biosimilar product itself and its specific indications and patient groups as well as any other international clinical use of the proposed biosimilar product. The safety monitoring program should be designed in a way that a differentiation between adverse events of reference and proposed product is possible, including any side effects not previously observed with the reference product. [160]

Sponsors are encouraged to discuss their intended post-approval safety monitoring program with the responsible FDA review division in order to satisfy product specific aspects. Information on the intended pharmacovigilance activities including risk management relevant information should be properly described and detailed, and must be provided together with risk management information to the FDA with the application file. Sponsors should also consider in their planning the possibility of additional post-approval surveillance, clinical studies or – trials, required to further assess rare safety risks such as serious immune reactions as it might be possible that rare safety risks may not be observed during the pre-approval clinical program. [60]

Similarly to the FDA, the EMA also focuses on post-approval safety monitoring programs and continued benefit-risk assessment to ensure the safety and efficacy of biotechnology-derived products. Like the US legislation, a pharmacovigilance

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[215] Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, April 2015, Guidance for Industry; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

[236] Regulation (EC) No 1901/2006, "Wheras" section (11); L 378/1, Official Journal of the European Union, 27.12.2006; http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

[237] VOLUME 2A Procedures for marketing authorisation Chapter 1 Marketing Authorisation, Annex I, Definition of a new active Substance; Revision 5, July 2015; http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/a/vol2a_chap1_201507.pdf

[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

[60] Immunogenicity Assessment for Therapeutic Protein Products; Guidance for Industry, August 2014; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf

system and a product specific risk management plan is required in accordance with the current EU legislation and guidelines on good pharmacovigilance practices. The risk management plan should consider and address identified and potential risks, e.g., immunogenicity, related to the use of the reference product within the post-approval phase and should also take into account any specific safety monitoring requirements required for the reference product or product class. The risk management plan, which details the intended risk management system of the proposed biosimilar product, must be provided together with information on all intended pharmacovigilance activities to the EMA with the application file. More information on the risk management plan can be found in the EMA Q&A to risk management guidance document. [238]

The safety monitoring program should be designed in a way that a clear identification by brand name and batch number of the pertained product and regarding its manufacturing is possible in case of any suspected adverse reactions. Of significant importance is the comparison of the type, severity and frequency of the known adverse reactions of the biosimilar product and the reference product. Like the US, applicants should consider the possibility of additionally required post-approval surveillance; clinical studies or - trials such as post-authorization safety studies (PASS) or post-authorization efficacy studies (PAES), required to further assess rare safety risks or efficacy and should take into account participation in running pharmaco-epidemiological studies conducted for the reference product. [57]

Monoclonal antibodies (EEA)

The basic approach for monoclonal antibodies is similar to that of biosimilar products that are not mAbs; namely, to amend routine pharmacovigilance activities with more proactive activities depending on the product. Thus, the applicant should provide information addressing his considerations on how to study the safety of the product in future with the application file. These considerations may address, for example: [1] (long term-) safety data in indications / conditions of use that have been extrapolated; [2] activities to gain additional immunogenicity data; and [3] monitoring of rare and serious adverse events documented and anticipated for the reference product. [200] Furthermore, it is recommended to monitor the developments regarding the automatic substitution of potentially interchangeable biosimilar mAb products at a national level. Such considerations should be part of the risk management plan.

<u>Quantity and type of scientific guidance documents for biosimilar products</u>

Currently, there are seven FDA guidance documents for biosimilar products which were first released as final or draft in 2014 and 2015. Two guidance documents address procedural issues; three of them address [1] scientific / overall regulatory

[238] Questions and answers on the risk management plan (RMP) summary, EMA/156738/2014, http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/05/WC500166101.pdf

[57] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev1, 18 December 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf

[200] Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues; EMA/CHMP/BMWP/403543/2010; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

issues, [2] quality considerations and [3] clinical pharmacological data. There is currently no product-class specific biosimilar product guidance available; for example, there is no mAb specific guidance. Two FDA guidance documents answer specific questions to biosimilar products (Q&A documents).

In contrast to the FDA, the EMA published the first biosimilar product scientific guidance documents in 2005/2006 and as of today there are several overall and different product-class specific documents (e.g., for somatropin, erythropoietins, or recombinant granulocyte-colony stimulating factor, etc.) developed and published. [239]

Three EMA scientific guidance documents for biosimilar products are available which address: [1] overall issues; [2] non-clinical and clinical requirements; and [3] quality considerations. All three documents are very similar in content to the FDA overall guidance documents for biosimilar products. Only one EMA product-specific guidance document for biosimilar mAbs is available which addresses non-clinical safety -and clinical safety issues. However, one further document is also relevant for biosimilar products and this addresses the immunogenicity assessment of mAbs. In contrast to the FDA, the EMA has not developed a guidance document yet, which specifically addresses the topic of clinical pharmacological data for biosimilar products.

14.2 Overall summary of overall safety relevant regulatory requirements

The following text summarizes the most significant safety relevant items mentioned above and outlines the identified differences between regulatory recommendations and legal provisions of both regions.

The overall definition of biological medicinal products is very similar. Both regions refer to the biological and living source of such products, and recognize the resulting product complexity and structure. In consequence, the thorough structural and functional characterization requires a higher testing effort than for chemically-synthesized products. However, the USA and the EU recognize that the characterization of biological medicinal products usually stays incomplete.

In the EEA, monoclonal antibody -and recombinant protein products are considered as biological medicinal products; however, these types of biological products are defined as “specified biological products” in the US-regulations. [27] In the USA, certain requirements are not applicable for “specified biological products” and these requirements can be waived in the Biologics License Application dossier. [219]

In the EEA, the Centralized Procedure is the applicable authorization pathway for biotechnology-derived products defined in the Annex of Regulation (EC) No

[239] Multidisciplinary: biosimilar, December 2016; http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c

[27] 21 CFR §601.2(a); April 2014; http://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol7/pdf/CFR-2014-title21-vol7-part601.pdf

[219] 21 CFR § 601.2(c)(1), April 2016; https://www.gpo.gov/fdsys/pkg/CFR-2016-title21-vol7/pdf/CFR-2016-title21-vol7.pdf

726/2004. In the USA, the applicable approval pathway for most biotechnology-derived products is the Biologics License Application. Both approval pathways require a comprehensive and full drug dossier including clinical data that must be submitted to the regulatory authority.

In contrast to the EEA, the generation of clinical data in the USA occurs in the centralized regulatory framework of an investigational new drug application and therefore is an inherent part of the application and review process with the FDA. [113] Thus, the FDA is involved in and familiar with the drug product at a very early stage of drug development. This differs from the process in the EEA where the approval process starts at a later stage with the submission of the dossier. This is because in the EU the generation of clinical data is neither a part of the application process, nor is there a centralized regulatory approach for clinical studies applied. Until the date of application of the clinical trials Regulation EU No 536/2014 clinical trials are decentralized regulated at a national level under Directive 2001/20/EC. [87] However, clinical trial data are reviewed by the EMA as well during the standard application review.

Both, the EEA and USA refer to the similarity to a reference product when defining the term “biosimilar”. While in the EEA, similarity to the reference product in quality-, biological-, safety- and efficacy related matters shall be established, the USA regulations require establishing a high similarity to the reference product in safety, purity and potency related matters. Furthermore, in the USA, the meaning of “highly similar” is explained with the absence of “clinically meaningful differences”. [30] [32] In this aspect the USA definition for the term “biosimilar” is more detailed and more stringent than that of the EEA.

The approval procedures for biosimilar products are only slightly different in the compared regions. Like for biological products, the Centralized Procedure is the mandatory approval pathway also for most of biosimilar products in the EEA. In the USA regulation, the approval pathway under 42 USC § 262(a) of the Biologics License Application was amended with subsection (k) which provides an abbreviated approval procedure for biosimilar products. Regarding the abbreviated dossier content (e.g., required testing and data), theoretically it could be less in volume with the approval procedure provided under 42 USC § 262(k); however, the FDA will determine the dossier content on a case-by-case basis. It should be noted that due to the small quantity of biosimilar products approved so far and corresponding minimal experience, it is not possible to provide more detailed information regarding the content and volume of a biosimilar product application dossier.

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[113] Code of Federal Regulations (Annual Edition 2014), 21 CFR 312.2(a); 21 CFR 312.2(b); http://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol5/pdf/CFR-2014-title21-vol5-part312.pdf

[87] Clinical trials - Regulation EU No 536/2014; General information section, European Commission, Directorate-General for Health and Food Safety, December 2016; https://ec.europa.eu/health/human-use/clinical-trials/regulation_en

[30] Guideline on similar biological medicinal products; CHMP/437/04 Rev 1, 23 October 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

[32] 42 USC §262 (i)(1), 42 USC §262 (i)(2)(A),(B); April 2015; http://uscode.house.gov/view.xhtml?req=%28title:42%20section:262%20edition:prelim%29%20OR%20%28granuleid:USC-prelim-title42-section262%29&f=treesort&edition=prelim&num=0&jumpTo=true

In the EEA, an abridged application procedure established with Article 10(4) of Directive 2001/83/EC for biosimilar products is also available. [126] However, within the EEA, biosimilar products such as recombinant monoclonal antibodies require a full application dossier in accordance with Article 8(3) of Directive 2001/83/EC. [84] In summary, an abbreviated procedure for biosimilar products is available in both regions. If, and how the procedure can be applied, depends on the proposed biosimilar products and its comparability to the reference product and need to be determined on a case-by-case basis.

There are no significant differences between the regions regarding the requirements of the reference product and to the use of a non-EEA / non-US licensed comparator product. Both, the EMA and the FDA allow the use of a non-EEA / non-US licensed comparator product to conduct certain non-clinical studies, but encourage the applicant to discuss such an approach upfront with them. Furthermore, the non-EEA / non-US comparator product must be authorized by a regulatory authority applying a similar regulatory and scientific level as the EMA and FDA applies. When using a non-EEA / non-US comparator, reliable bridging data involving all three products (proposed biosimilar product, EEA- or US- reference product, and non-EEA or non-US comparator product) must be provided. The similar approach to the use of a non-EEA / non-US comparator product has the advantage that the development program for the proposed biosimilar product may be used for both, the EU authorization and the US filing; however, such bridging data may adulterate safety relevant data (e.g., thru potential bias). Specifically the FDA Q&A guidance document discusses the topic of using a third-party comparator product and providing more detailed information than the relevant EMA guidance documents. [215]

In contrast to the EU legislation, the US-American federal law provides the possibility to provide a biosimilar product with an interchangeable status which allows an approved interchangeable biosimilar product to get substituted at the pharmacy level. [223] However, it remains at state level to enforce the federal law on automatic substitution in the individual US states. The US states may add specific requirements to the US law on automatic substitution when enforcing the US law at state level. Further, there is nothing to stop any state from writing a state law that contradicts US law. Determining a biosimilar product as interchangeable within in EEA region is at a national level. Further, the EMA has neither the authority to determine a biosimilar product to be interchangeable / substitutable, nor are there appropriate regulation / legislation in place at the Union level. The lack of a centralized and EU-regulated determination on interchangeability and automatic substitution leads to individual national solutions which negatively impact

[126] Directive 2001/83/EC of 6 November 2001, Article 10(4); OJ L 311, 28.11.2001, p. 67, Consolidated version 16/11/2012; http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[84] Directive 2001/83/EC of 6 November 2001; Article 8; Article 8(i); OJ L 311, 28.11.2001, p. 67, Consolidated version 16/11/2012; http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[215] Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, April 2015, Guidance for Industry; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

[223] 42 USC §262(i)(3), April 2015; http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title42-section262&num=0&edition=prelim

pharmacovigilance activities through the lack of proper and clear biosimilar product identification and traceability / tracking systems.

Regarding the prescriptions information for biosimilar products and interchangeable biosimilar products, neither the EMA nor the FDA provides a final solution here. Directive 2012/52/EU requires the brand name instead of INN for biological products, however no information to biosimilar products is provided. In the US, no difference between medicinal products and biosimilar products is made regarding to the prescription information. Either the proprietary name or nonproprietary name shall be provided on the prescription. To avoid prescription errors, to improve traceability, and to facilitate pharmacovigilance activities information to biosimilar products and interchangeability should be described properly in prescriptions.

While the exclusivity period in the US-market is 12 years, it is typically 10 years with the EEA with the Centralized Procedure. [161] [201] This allows biosimilar products to be available for patients two years earlier in the EEA than in the US; however, there is also two years less market and pharmacovigilance experience with the reference product.

The naming and labeling of biosimilar products, especially for interchangeable products, is still an open item in both regions that need to be addressed. While the FDA is already working on the remaining issues regarding interchangeable products; the WHO just published a solution on the naming of biological products. And, while the FDA has issued a guidance document about the labeling of biosimilar products, a similar guidance document is not available in the EEA.

The use of a different container- / closure- or delivery device system than the reference product owns is allowed for biosimilar products in the EEA if the impacts to the product are properly justified. The EMA guidance document does not provide any further information, especially to additional testing's (e.g., leachable profile). In contrast to the EMA, the FDA accepts only minor deviations and these only if certain conditions are met. For interchangeable products the FDA regulations are even more thorough. The FDA guidance document provides detailed information on the topic including additional testing and informs about the non-applicability of the US Pharmacopeia *"Elastomeric Closures for Injections".* With adequate testing, a different formulation than the reference product uses can be used for the biosimilar product in both regions.

Unlike the requirements in the FDA regulation, biosimilar products are waived from pediatric assessment requirement in the EEA.

Basically, there are no significant differences in pharmacovigilance system related matters and regulatory recommendations between the two regions; however compared to the FDA counterpartying guidance document, the EMA provides very detailed information on what needs to be addressed in the RMP regarding

[161] 42 USC §262(k)(7)(A), 42 USC §262(k)(7)(B); October 2015; http://uscode.house.gov/view.xhtml?path=/prelim@title42/chapter6A/subchapter2/partF/subpart1&edition=prelim

[201] EMA Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications; EMA/940451/2011; http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125166.pdf

immunogenicity. [61] For mAbs the relevant EMA guidance document recommends monitoring the developments regarding the substitution of potentially interchangeable biosimilar mAb products at a national level and recommends addressing this in the risk management plan as well. The FDA encourages the applicants to discuss the intended pharmacovigilance system with the agency.

Overall, it is of note, that the amount and scope of regulation is very similar as the same topics are covered by the relevant guidance documents. There exist some differences in the overall safety relevant regulatory requirements between the two regulatory regions although most items are addressed similarly. The unresolved issues of biosimilar product identification, traceability, labeling and naming, and the prescription information of interchangeable biosimilar products may impact the safety of such biosimilar products in the EU and the USA. Different regulatory requirements regarding the reference container closure system and the extent of accepted deviations and different testing requirements (e.g., leachables testing) in the two regions may result in different product safety. The use of a non-EU / non-US comparator product may impact the biosimilar product safety in both regions since the bridging data that enable the comparison of all three products involved, may pose a risk of potential bias which could produce incorrect safety data.

Regarding the quantity and type of scientific guidance documents for biosimilar products published by the FDA and the EMA, it is observed, that the FDA has impacted development in this sector by delaying the provision of scientific guidance documents. However, the FDA guidance documents that are available now are very similar to the EMA guidance documents in overall content and type. Nevertheless, both the EMA and the FDA should continue developing overall and product-class specific scientific documents to topics like: [1] quality considerations for mAbs; [2] clinical trials and PASS with biosimilar products; [3] extrapolation of safety, efficacy and immunogenicity data across indications; [4] comparability of biosimilar products after a change in the manufacturing process, etc.

14.3 Analysis of the non-clinical safety considerations

USA

The FDA scientific considerations guidance document addresses non-clinical safety considerations such as non-clinical testing strategies, general approaches and clinical safety considerations. [160] The FDA quality considerations guidance document also addresses non-clinical safety requirements and testing but does not address clinical safety requirements. [159]

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[61] Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins; EMEA/CHMP/BMWP/14327/2006 Rev1; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/10/WC500194507.pdf

[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

[159] Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; Guidance for Industry; April 2015;

The FDA uses the “Totality-of-the-Evidence” approach to assess the demonstration of biosimilarity. This approach is described in great detail in the scientific guidance documents. Also described in detail is the development of data necessary to facilitate a demonstration of biosimilarity with a focus on the structural characterization of the product. The guidance documents also provide information on quality considerations for non-clinical tests, especially to comparative analytical studies by providing information to physicochemical characterization, functional activities, receptor binding and immunochemical properties, impurities, tests on the finished drug product and stability testing. [159]

The FDA recommends a stepwise approach to developing the data needed to demonstrate biosimilarity. The goal is to establish comparable data that demonstrate that there are no clinically meaningful differences between the proposed biosimilar product and the reference product regarding safety, purity, and potency. Thus, the sponsor should evaluate the extent of residual uncertainties regarding biosimilarity after each step and should address these uncertainties in the next step. [160] The stepwise testing approach facilitates a target-oriented approach to non-clinical and clinical studies.

The FDA reserves the right to determine the type, amount and necessity of non-clinical and clinical testing, including immunogenicity data on a case by case basis necessary to sufficiently demonstrate biosimilarity. The FDA also encourages the sponsors to discuss their planned biosimilar development program early with the FDA.

Extensive and robust structural and functional characterization of the products to be compared is the first step of the approach. For this comprehensive product characterization, suitable in-vivo and in-vitro studies according to the latest technology should be used to qualitatively and quantitatively detect differences in characteristics of the compared products. [160] It should be demonstrated within the structural and functional characterization that the expression construct of the comparators are highly similar in encoding with basically the same primary amino acid sequence except for minor modifications (e.g., N- or C-terminal truncations). Additionally, the [1] primary- (e.g., amino sequence), [2] secondary-, tertiary-, and quaternary structures; [3] post-translational modifications (e.g., glycosylation); [4] biological activities; [5] any other variations; and [6] intentional chemical modifications (e.g., pegylation) of the comparative products should be physico-chemically evaluated and compared. [160] The physicochemical and biological characterization of the two compared products should be performed with an appropriate number of multiple lots to see the lot-by-lot variability. Both, lots intended for clinical study purpose and lots of the proposed product intended to be

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http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf

[159] Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; Guidance for Industry; April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf

[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry; April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

marketed should be used for comparability demonstration with the reference product. [160] The analysis should also include evaluation of excipients, purity, impurities (e.g., process and product related), and stability of the final formulation of the proposed product and the reference product. If one of the compared products cannot be characterized in a sufficient manner, a change of the approval pathway should be discussed with the agency.

The analytical structural and functional comparison should be followed by steps [2] animal data investigating toxicity; [3] comparative clinical human PK- and PD studies; [4] clinical immunogenicity; and finally in case of any residual uncertainties regarding biosimilarity [5] targeted comparative clinical studies to gather additional clinical data in safety and effectiveness. [160]

Outcomes from animal toxicity studies are more suitable to support a comparative safety evaluation than to demonstrate biosimilarity. The safety of the proposed product may be supported with comparative animal toxicity testing data (including animal pathology, histopathology, PD / PK- and immunogenicity studies) prior to the initiation of human clinical studies in such cases where the outcome of the previous steps (structural and functional characterization) was not sufficiently meaningful and where safety concerns of the proposed biosimilar product remain. [160] Limited animal toxicity data (if a relevant animal model is available) may be adequate to facilitate initial clinical use assuming comparative structural and functional data have adequately demonstrated analytical similarity between the two products [160]. The FDA scientific considerations guidance document refers to the ICH guideline document for industry S6 (R1) regarding the design of animal toxicology studies and limitations of such studies. [160] Sponsors are encouraged to discuss their intended development plans, including any plans and justifications regarding animal toxicity studies at an early date with the FDA.

Safety data generated from animal toxicity studies are not necessary when clinical data (e.g., from non-US- markets) are available. If a relevant animal species for the proposed product is not available, animal toxicity studies are not adequate to gather pharmacologically relevant data. [160] Instead, additional comparative in-vitro studies using human cells or tissues shall be performed to obtain data on potential clinical effects. When the data that were generated during the structural and functional characterization demonstrate high similarity between the two products, reference product and biosimilar product, then, non-clinical safety pharmacology, reproductive and developmental toxicity and carcinogenicity studies are not required. [160]

With respect to the use of animal PK- and PD- measures, the scientific consideration guidance indicates that a comparative single-dose animal study using PK and PD measures could support a demonstration of biosimilarity. However, the use of such study will not make human PK- and PD studies unnecessary.

Animal immunogenicity studies are not adequate to detect potential immune reactions to protein products in human individuals. Nevertheless, differences in manufacturing between the compared products may lead to varied immunogenicity

[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry; April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

and therefore anti-protein antibody response measurements in animals could provide helpful information. Also, differences noticed during immunogenicity assessments in animals may point to potential differences in structure or function not captured in the previous testing but relevant to human safety. [160]

EEA

There are three relevant EMA guidance documents: [1] similar products guidance document, [2] similar products – non clinical and clinical issues guidance document, and [3] similar products- quality guidance document. [30] [57] [199] These EMA guidance documents address general approaches, non-clinical safety considerations as well as clinical safety topics, including immunogenicity.

The product specific EMA guidance document on biosimilar mABs to non-clinical and clinical issues is also relevant as this document address requirements for biosimilar monoclonal antibodies. [200]

Like the FDA, the EMA considers the full and complete set of comparative data in the assessment of the demonstration of biosimilarity. The goal of the comparability program is to establish similarity to the reference product concerning quality attributes, biological activity, safety and efficacy based on extensive and comparative testing data. [30]

In developing the non-clinical comparative data needed, the EMA also recommends the use of a stepwise testing approach. The process begins with extensive and robust structural and functional testing and includes characterizing the physicochemical and biological product properties using the latest state of the art orthogonal analytical methods and testing in-vitro- and in-vivo. The comparative physicochemical and biological characterization of the compared products should be performed with an appropriate quantity of batches intended for clinical use and commercialization. The outcome of the physicochemical characterization should provide data for example to: [1] the primary and higher order structures of the tested product; [2] the target amino acid sequence; [3] the N- and C-terminal amino acid sequences and SH groups; or [4] any post-translational modifications; and as well as [5] any variations related to the used expression system, etc. [199]

The outcome of the biological assessment under use of biological assays should provide data to the biological activity. In addition, the purity and impurity profiles of the compared products should be investigated.

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[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry; April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

[30] Guideline on similar biological medicinal products; CHMP/437/04 Rev 1, 23 October 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

[57] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev1, 18 December 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf

[199] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1); EMA/CHMP/BWP/247713/2012, Rev.1; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167838.pdf

[200] Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues; EMA/CHMP/BMWP/403543/2010; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

Then, depending on the level of evidence achieved in the structural and functional characterization, subsequent non-clinical and clinical studies are necessary to be conducted. The amount of these studies may be more or less extensive. The goal of the in-vitro studies is to gather data that allow the analysis of the concentration – activity / binding relationship of the two products at the pharmacological target(s). [57] It should be noted that in-vitro assays are considered more suitable for non-clinical comparability testing than animal studies due to their higher sensitivity and specificity.

After evaluation of the in-vitro study results, and depending on the extent of evidence these data have provided, the need for in-vivo studies in a species relevant animal model should be determined. If a species relevant model does not exist, the applicant may generate the necessary data in human studies. Typically, an in-vivo animal study is not necessary when data from the previous steps [1] product property characterization and non-clinical in vitro studies, and [2] determining the need for in-vivo studies, are adequate and without any identified issues. [57]

Safety data generated from standard repeated dose toxicity studies in non-human primates, and toxicity studies in non-relevant species are not recommended. Non-clinical safety pharmacology, reproductive and developmental toxicity and carcinogenicity studies are not necessary, and local tolerance studies are normally not required assuming no unknown or not well known excipients are involved with the intended route of administration. Generally, a flexible approach should be applied for safety studies.

Immunogenicity assessment is considered an integral part of the comparability program. However, animal immunogenicity studies are not adequate to detect potential immune reactions to protein products in human individuals. Nevertheless, such study data may help in interpreting in-vivo animal data and thus blood samples should be taken and stored.

If the outcome of the biosimilar comparability program cannot demonstrate biosimilarity with the reference product, the applicant should consider the alternative approval pathway of a full marketing authorization application.

Non-clinical specifics for similar monoclonal antibodies (EEA)

The guidance on non-clinical and clinical issues of monoclonal antibodies also recommends a stepwise approach to be applied to non-clinical testing. The extent and nature of non-clinical and clinical studies may vary depending on the outcome of the previous characterizations testing. [200] The selection of the in-vitro and in-vivo studies to be conducted varies from case to case, but the process should begin with investigating the specifics on binding or function within a comparative in-vitro testing. The EMA guidance document describes the testing in three steps:

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[57] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev1, 18 December 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf

[200] Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues; EMA/CHMP/BMWP/403543/2010; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

1. Step 1 provides information on the assays that should be included in the in-vitro non-clinical study; such as assays assessing immunological functions (e.g., product binding affinity to the intended target and receptors), induction of Fab- and Fc-associated effector functions. An assessment of ADCC and CDC is not needed when the concerned mAbs are directed against non-membrane bound targets. [200]
2. Step 2 provides information that shall help determining the need for in-vivo-studies that includes considerations of any unidentified quality attributes of the reference product (e.g., new post-translational modification structure), different quantity of quality attributes between the comparators, or varying formulations (e.g., application of excipients typically not used for mAbs). [200]
3. Step 3 provides the same information on in-vivo testing as the overall document similar products – non clinical and clinical issues guidance. If further in-vivo testing is necessary, a relevant animal model should be identified as toxicological data gathered from non-human primates are typically not useful.

14.4 Overall summary to non-clinical safety considerations

The following text summarizes the most significant safety items mentioned in the scientific recommendations to the non-clinical safety requirements of both the USA and the EU.

In both regions, the EU and the USA, extensive comparability testing using sensitive equipment and according to the latest technology is necessary to characterize physicochemical and biological product properties in order to demonstrate biosimilarity of the proposed biosimilar product to the chosen reference product. In order to allow a structured and well comparative testing program and generation of comparative data, a stepwise approach is generally recommended from both regulatory authorities. For the evaluation of the non-clinical data, the same totality of comparability data approach is used which is also used to evaluate the biosimilarity between the compared products.

Animal toxicity testing and animal immunogenicity studies are usually not recommended and considered as useful. Non-clinical safety pharmacology, reproductive and developmental toxicity and carcinogenicity studies are typically not required. However, both the USA and the EU recognize that animal immunogenicity data could be helpful in interpretation of animal in-vivo studies or in evaluation of differences in production processes.

Overall the scope of regulation is very similar as the same topics are covered by the relevant guidance documents. It is noted, that the FDA scientific considerations guidance document provides more detailed information with respect to the totality-of-evidence approach and structural analysis than the EMA guidance documents. The FDA guidance documents are also more clearly arranged than their EMA counterparts. Further, while detailed information on the structural product

[200] Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues; EMA/CHMP/BMWP/403543/2010; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

characterization is provided together with other relevant information in the mentioned FDA scientific considerations guidance document, the EMA splits the information into two documents, in the similar products – quality guidance document and the similar products – non clinical and clinical issues guidance document. In contrast to the EEA, there is no product-specific FDA guidance document that addresses the non-clinical and clinical specifics of biosimilar monoclonal antibodies.

14.5 Analysis of the clinical safety requirements

Various scientific guidance documents on clinical safety requirements are available in the USA and the EU.

USA

The FDA addresses clinical safety considerations with the scientific considerations guidance document, the clinical pharmacology guidance document and immunogenicity assessment guidance document. [160] [214] [60]

For clinical safety evaluation, the FDA recommends a stepwise and progressive approach. The first step begins with comparative human PK- and PD- measures along with clinical immunogenicity assessment. This is followed by additional comparative clinical studies, such as clinical safety; or clinical efficacy studies, when needed due to address residual uncertainties about biosimilarity. [214]

Comparative clinical human pharmacology studies (PK/PD) including immunogenicity assessment, represent a critical part of demonstrating biosimilarity, and typically, the FDA expects the results of such studies to properly demonstrate biosimilarity. If the outcomes of the comparative human PK- / PD- studies show a meaningful correlation between PK- / PD-results and clinical effectiveness, comparative efficacy studies may be skipped. [160]

The selected PK- and PD-parameters, including their selection criteria should be predefined. Also, the selected PK- and PD-study population shall be scientifically justified; this also applies to the selected study dose and chosen route of administration. Furthermore, the selection of PD- parameters should be orientated on: [1] the relevance to clinical outcomes; [2] the ability to ensure appropriate precision; and [3] the necessary sensitivity to detect clinically meaningful differences. [160] The FDA recommends a crossover designed study for PD- studies for products with a short half-life (e.g., < five days). A parallel study design is recommended for products with a long half-life (e.g., > five days). [160]

The FDA´s clinical pharmacology guidance document addresses questions that a sponsor may have regarding the design and use of clinical pharmacology studies.

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[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

[214] Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, Guidance for Industry; Guidance for Industry, December 2016; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf

[60] Immunogenicity Assessment for Therapeutic Protein Products; Guidance for Industry, August 2014; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf

The guidance provides detailed information on three concepts that need to be considered in the use of clinical pharmacology studies: [1] exposure and response evaluation; [2] assessment of remaining uncertainty; and [3] suppositions about analytical quality and similarity. It further discusses adequate bio-analytical methods used for PK- and PD-assessments and general and specific assay considerations. [214] The guidance document provides very detailed information to critical study design issues such as study population, dose selection, route of administration, PK- and PD- measures, sampling strategy, etc. In certain cases it is desirable to increase the sensitivity for detecting differences. This may be desired e.g., when a product can only be administered to patients and if the approved dose results in nonlinear PK or exceeds the dose needed for maximal PD- effect. In such a case, the FDA provides the possibility of the selection of an alternative dosing scheme, e.g., a single dose for a chronic indication or a lower dose than the approved dose, provided that their appropriateness is scientifically justified and submitted to the FDA. [214] The FDA encourages the sponsors to discuss the clinical pharmacology development plan upfront with them.

Immunogenicity assessment

All three FDA guidance documents mentioned above address the clinical immunogenicity assessment topic in some way. Clinical immunogenicity assessment is considered a key element in the demonstration of biosimiltarity. To assess and mitigate immunogenicity, a risk-based approach should be applied. [60] In consequence, one comparative clinical study investigating immunogenicity is expected by the FDA at a minimum since non-clinical immunogenicity testing in animals is of low predictive value due to different immune responses in human and animal immune systems. [160] Furthermore, additional pre- and / or post-approval surveillance or studies may be considered to further assess immunogenicity. A comparative parallel designed study (e.g., a head -to-head study) in subjects that have not been previously exposed to the (reference-) product but for whom the product is indicated is recommended to evaluate clinical PK- and PD- similarity including immunogenicity assessment. The FDA expects the sponsors to proactively define and discuss the clinical immune response criteria by defining significant clinical incidents for each type of potential immune reaction (e.g., anaphylaxis, neutralizing antibody formation) using established criteria where available. The length of the follow-up period shall be described in detail and depends on several factors like: [1] the time duration for the generation of immune reactions and clinical sequelae; [2] the time duration until disappearance of the immune reactions and clinical sequelae following interrupting therapy; and [3] the length of administration.

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[214] Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, Guidance for Industry; Guidance for Industry, December 2016; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf

[60] Immunogenicity Assessment for Therapeutic Protein Products; Guidance for Industry, August 2014; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf

[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

For chronically administered products a follow-up period of at least one year is recommended. [160]

The FDA also allows for the possibility to extrapolate immunogenicity findings for one condition of use to other conditions of use. In order to do this, the sponsor should use an adequately sensitive study population and treatment scheme in order to prognosticate distinctions in immune reactions between the compared products across the indications. [160] Each additional indication that is sought through extrapolation should be scientifically justified. [215]

The FDA immunogenicity assessment guidance document applies to biological products and biosimilar products. The document describes clinical consequences of and the immunogenicity influencing patient- and product specific factors in great detail. [60] It also provides recommendations to address these issues and outlines a risk-based approach in order to evaluate and mitigate the risk of unwanted immune reactions in the clinical phase. Further, it outlines that assays used in routine lot release and stability testing should be validated.

With regard to the risk mitigation the FDA document provides information on the evaluation of clinical relevant immune reactions that includes:

1. Assays for anti-drug antibody
   Sensitive assays for anti-drug antibody (ADA) should be developed and levels of protein product in the sample should be assessed at the same time; [60]

2. Sampling considerations
   For product-specific antibody testing collecting baseline samples is recommended and the anticipated intended use of the protein product should be considered in determining the post-baseline sampling frequency and period. During the initial phase of use a more frequent sampling is recommended for new, chronically administered products and a less frequent sampling after ongoing use. The duration of repeat sampling periods should be sufficient to determine the type of immune reaction (e.g., persistent, neutralizing, or linked with clinical long-term complications). In order to define the clinical relevance of anti-drug antibodies unscheduled sampling, initiated by suspected immune related adverse events, should be performed supplementing the pre-specified sampling schedule. Blood samples should be taken and banked for future testing; [60]

3. Dosing
   Regarding the dosing, the FDA recommends a conservative approach for first-in-human-trials with graded dosing between individuals and dosing

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[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

[215] Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, April 2015, Guidance for Industry; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

[60] Immunogenicity Assessment for Therapeutic Protein Products; Guidance for Industry, August 2014; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf

cohorts. Further, sufficient time intervals among dosing cohorts and among individuals within a dosing cohort as well as prespecified dose escalation criteria is recommended; [60]

4. Adverse events
   In high-risk situations, the FDA recommends more intensive monitoring, such as investigating the development of unwanted antibodies through real-time assessments prior additional dosing. Further, if clinically relevant immune responses are detected, these should be investigated and the underlying mechanisms and contributing factors identified; [60]

5. Comparative immunogenicity studies
   The FDA recommends preparing a justification including predefined criteria that rationale the extent on differences in incidence or severity of immune reactions considered unacceptable for the safety of the biotechnology-derived product; [60]

6. Postmarketing monitoring of product safety
   Postmarketing safety monitoring should be robust and be adjusted to the specifics of the biotechnology-derived product. Therefore, the FDA recommends discussing the intended postmarketing safety monitoring approach with the FDA. Further postmarketing clinical studies may be required to assess rare, but potentially serious side effects, which were not detected during pre-approval clinical testing because of an inappropriate study size. [60]

The Appendix A of the FDA immunogenicity assessment guidance document provides information to: the [1] Diagnosis of Anaphylaxis; [2] Cytokine Release Syndrome; [3] Non-Acute Immune Responses; [4] Antibody Responses to Therapeutic Protein Products; [5] Utility of Animal Studies; and [6] Comparative Immunogenicity Studies in great detail. [60]

There is no specific FDA guidance document for monoclonal antibodies that addresses immunogenicity assessment, non-clinical issues or clinical issues. However, in the clinical pharmacology guidance document and the immunogenicity assessment guidance document, certain aspects specific to mAbs are considered in a manner similar to the EMA guidance document on mAbs. [214] [60]

Comparative clinical studies

Comparative clinical studies will be necessary when after the outcomes of the previous steps structural / functional characterization, animal testing, human PK- / PD- data, and clinical immunogenicity assessment still uncertainties remain about clinically meaningful differences between the compared products or when specific

[60] Immunogenicity Assessment for Therapeutic Protein Products; Guidance for Industry, August 2014; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf

[214] Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, Guidance for Industry; December 2016; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf

aspects and prior experiences related to the safety or efficacy of the reference product or its product class require additional clinical study data. [160]

To conduct a comparative clinical study, a comparative equivalence trial design with symmetric inferiority and superiority margins would be typical to establish the necessary statistical evidence. [160] The chosen study endpoints should be capable of determining clinically meaningful differences between the two compared products. The study duration, study population and study sample size should be sufficient to allow the detection of clinically meaningful differences between the compared products, including any relevant safety signals (e.g., immune responses). If this is not possible within a single comparative study, any safety and immunogenicity related signals may be investigated in a separate study. [160]

Overall, all study related key factors (e.g., design, population, endpoints, size, margins, etc.) should be scientifically justified and discussed with the FDA prior to study initiation. Ideally, clinical trial data should be generated with biosimilar products derived from the commercial manufacturing process.

If the biosimilar product in the application fulfills the regulatory requirements under section 351(k) of the PHS Act, the FDA provides the possibility to extrapolate clinical data across indications. This means that safety, purity, and potency information for one or more additional indications for which the reference product is approved may be extrapolated to and applied for the proposed biosimilar product. [160] The prerequisite is that the applicant of the biosimilar product demonstrates biosimilarity of its product to the reference product in one condition of use for which the reference product is licensed. However, each indication that is sought additionally must be scientifically justified, and one indication must be studied that provides clearance for successive extrapolation of clinical data to other indications. Therefore, the FDA recommends studying an indication sensitive enough to detect clinically meaningful differences between the compared products. [215] Factors that need to be considered and scientifically justified in order to extrapolate such data include information about the proposed biosimilar product with respect to: [1] the mode of action in each additional indication; [2] PK/PD-data; [3] Immunogenicity data; [4] possible differences in toxicity for the additional indications; and [5] other factors that could influence safety or efficacy. [160]

EEA

The EMA addresses general approaches, clinical considerations (e.g., pharmacokinetic, pharmacodynamic, and efficacy studies) and clinical safety topics including immunogenicity of biosimilar products in the EMA´ scientific guidance

[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

[215] Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, April 2015, Guidance for Industry; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

document on similar products – non clinical and clinical issues. [57] The product specific document similar products mAb guidance addresses the mentioned requirements for monoclonal antibodies. [200]

There are no scientific guidance documents that specifically address the immunogenicity assessment for biosimilar products available. The available EMA guidance document on immunogenicity assessment and the guidance document on the immunogenicity assessment of monoclonal antibodies address the immunogenicity topic of biological products. [61] [204] These guidance documents apply for biological products but are applicable to biosimilar products as well.

Like the FDA, the EMA recommends that clinical evaluation be performed in a stepwise approach that begins with pharmacokinetics (PK) and, if needed, pharmacodynamic (PD) studies. Next, clinical efficacy and safety trial(s) should be performed, or if necessary, confirmatory PK / PD trials. Ideally, clinical study data should be generated with biosimilar products derived from the commercial manufacturing process.

Comparative pharmacology studies typically represent an essential role in demonstrating biosimilarity, and data should normally being provided. [57] The selected PK- parameters should be predefined and their limits scientifically justified. It is possible to skip a pivotal PK- study in the target population if previous in-vitro study data have demonstrated comparable product-target(s) interaction, and continuing PK- data are gathered during further studies (e.g., safety-, efficacy-, or PD- studies). [57] The EMA recommends a single dose cross-over study be performed including a complete pharmacokinetic characterization and data of the late elimination phase in a sensitive population (e.g., populations with fewer human factors that might cause variations between individuals). A parallel group design is recommended for products with a long half-life and / or high incidence of immune reactions. PK- studies should be used to collect immunogenicity data through anti-drug antibody measurements.

The choice of PD- markers used in PD- studies depend on their ability to demonstrate the intended clinical result. PD-measures should be performed together with PK- studies where possible. In some cases, the results of comparative PK-/PD- measures may be adequate to demonstrate clinical comparability between the compared products when certain requirements are met such as:

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[57] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev1, 18 December 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf

[200] Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues; EMA/CHMP/BMWP/403543/2010; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

[61] Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins; EMEA/CHMP/BMWP/14327/2006 Rev1; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/10/WC500194507.pdf

[204] Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use; EMA/CHMP/BMWP/86289/2010; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128688.pdf

[57] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev1, 18 December 2014; ; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf

[1] PD- marker is a widely recognized surrogate marker that can be correlated to patient results;

[2] PD- markers are adequate to demonstrate pharmacological action of the active substance and a clear relationship of dose-response or concentration-response. If so, a clinical efficacy study may be waived provided that the results of a single or multiple dose-exposure-response study at two dose levels minimum provide sufficient data;

[3] Previous testing steps provide strong and robust data in such a manner that biosimilarity can be well demonstrated. In such cases a confirmatory clinical trial may be skipped. [57]

Efficacy studies may be necessary in order to confirm similar clinical performance between the compared products, when surrogate markers are not available. The comparative efficacy study design should be a randomized equivalence parallel group trial design, ideally double-blind with the use of efficacy endpoints and in an adequately sized patient group, or in models sensitive enough to identify safety- and efficacy related discrepancies. A non-inferiority trial design could be used with proper justification. Product-class-specific EMA guidance provide information on efficacy endpoints; otherwise, sensitive clinical models and study conditions should be used in order to detect safety and efficacy issues. Typically, pre-defined and justified comparable margins are needed to establish statistical and clinical evidences. The relevant ICH- and EMA guidance documents should be consulted to help choosing comparable margins.

A confirmatory clinical study may be unnecessary in cases where the data from the structural and functional characterization as well as data from the PK- and/or PD-profile are able to clearly demonstrate similar efficacy and safety, providing that the impurity- and excipients profiles are acceptable. [30] [57] The EMA should be involved if the sponsor determines that a confirmatory clinical study is not necessary.

Clinical safety adverse reactions between the compared products should be monitored and quantified in type, severity and frequency. This includes adverse reactions already known and described for the reference product. Immunogenicity is the most significant issue to consider in clinical safety. Immunogenicity studies should be comparative in nature, and their duration should be determined on a case-by-case basis. The length of the follow-up period depends on several factors like length of administration and types of unwanted immune reactions known from the reference product. The follow-up period should be justified accordingly. A follow-up period of at least one year is required in the pre-authorization phase for chronically administered products, but a shorter period (e.g., 6 month) might be possible with adequate rationale. [57]

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[57] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev1, 18 December 2014; ; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf

[30] Guideline on similar biological medicinal products; CHMP/437/04 Rev 1, 23 October 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

Once the biosimilar product has successfully demonstrated biosimilarity in one indication of the reference product, it is possible to extrapolate clinical data on safety and efficacy to other indications of the reference product if properly justified. [30] However, additional data may be required when the relevance of the confirmed safety and efficacy data for the indications sought is vague, or when the active substance of the reference product: [1] interacts with various receptors that may affect the indications; [2] has multiple active sites which may affect various indications; or [3] the studied indication is improper for the indications sought in question of safety and efficacy. [57] In order to extrapolate immunogenicity data from the confirmed indication to other indications of the reference product, the EMA requires proper justification and additional data may be needed. [57] It should be noted, that after a biosimilar product has received marketing authorization, further changes to the manufacturing process of the biosimilar product do not require the repeat of biosimilarity demonstration to the reference product according to the regulation. [30]

Clinical specifics for similar monoclonal antibodies (EEA)

The similar products mAb guidance document also recommends a stepwise approach to the clinical testing. [200] A pharmacokinetic study serves as the first step in the clinical data development to establish similar efficacy and safety. The study population should be homogeneous and sensitive enough to detect any potential differences. Therefore, a single dose study in healthy subjects is to prefer due to the less variability in PK. The rationale for the choice of the patient population for the PK- study shall be documented. The EMA recommends a parallel group design to assess pharmacokinetics due to the long half-life of mAbs and the potential incidence for immune reactions. A single dose cross-over study with complete identification of the PK-profile and data of the late elimination phase is recommended for mAbs with short half-life. PK- studies should be used to collect immunogenicity data through anti-drug antibody measurements. [200]
Like other biosimilar products that are not mAbs, the comparability of the PK-profiles should have been investigated in the previous non-clinical testing. However, in some cases (e.g., when the PK of the mAb is highly variable even in the same indication), it may make more sense to investigate the PK in a comparability clinical efficacy trial because only that involves enough subjects to demonstrate equivalence of PK. If a comparative clinical efficacy trial is intended that includes PK- assessment without prior comparative PK- evaluation and human exposure of the biosimilar mAb, this should be properly and individually justified, especially when only limited non-clinical in vivo data are available. [200]

Pharmacodynamic parameters may help to establish comparability for some mAb products and indications. For the purpose of establishing overall comparability, the

[57] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev1, 18 December 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf

[30] Guideline on similar biological medicinal products; CHMP/437/04 Rev 1, 23 October 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

[200] Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues; EMA/CHMP/BMWP/403543/2010; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

use of multiple PD- markers is preferred. Where no specific PD endpoints are available, data of non-clinical PD- assessments such as in-vitro testing data should be used accordingly. When PD- markers are intended to be used as pivotal evidence to demonstrate comparability, the dose-concentration-response relationships or time-response relationships should be investigated as this may successfully generate evidence of comparability if the selected doses are within the linear part of the dose-response curve. The risk of developing anti- mAb antibodies should always be considered. [200]

Clinical efficacy trials are necessary if the results of the comparative PD- studies were not sufficient to demonstrate clinically comparability between the compared products. The design of comparative efficacy studies should be a randomized equivalence parallel group trial design, ideally double-blind with the use of the clinical endpoint (and, if required, any additionally implemented measures) and with a clinical model or patient population sufficient in size and sensitive enough to identify safety- and efficacy related discrepancies between the two compared products. Pediatric clinical studies are typically not required for biosimilar products as the goal of the development program is to establish comparability thus, the focus in selecting the primary patient population is laid on homogeneity and sensitivity. [200]

In order to further evaluate the comparability of the clinical safety, the type, severity and frequency of the adverse reactions of the comparators should be compared with a focus on the adverse reactions previously documented for the reference product. Where PD- markers were used as pivotal evidence to demonstrate comparability, adequate data should be provided in order to confirm similar clinical safety and immunogenicity. The rationale for the length of the follow-up period pre-authorization should be documented.

Because it is nearly impossible to detect rare but serious adverse events like progressive multifocal leukencephalopathy within the pre-authorization phase, applicants may choose to collect additional safety data post-authorization (e.g., through PASS). Such activities need to be discussed and detailed in the risk management plan (RMP) submitted with the product application. The RMP should also provide information on how to evaluate and monitor clinical safety in re-treatment conditions (e.g., chronically administered mAbs).

For immunogenicity assessment purpose, a systematic and comparative evaluation of immunogenicity is required to identify possible clinical consequences (e.g., loss of efficacy). In order to detect anti-drug antibody development, the best suitable approach in terms of the best population and administered dose (e.g., population PK- approach in patients or healthy subjects; inhibition of antibody development in high doses) should be explored.

It is possible to extrapolate clinical data, including immunogenicity data, to other indications / conditions of use of the reference mAb, if properly justified and based on the results from a successful comparability exercise. However, where PD-markers were used to establish pivotal evidence demonstrating comparability, and

[200] Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues; EMA/CHMP/BMWP/403543/2010; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

when different mechanisms of action apply to the claimed indications or in case of any other existing uncertainties, further data are needed to support extrapolation for each indication sought additionally. [200] Appropriate postmarketing activities monitoring the clinical safety of the indications to which safety and immunogenicity data have been extrapolated should be described in the RMP and provided with the application dossier.

Immunogenicity assessment

The available EMA guidance document on immunogenicity assessment provides guidance on non-clinical and clinical issues. [61] Like the FDA, the EMA considers clinical immunogenicity assessment as a key element in the biosimilarity demonstration since non-clinical immunogenicity testing is of low predictive value due to different immune responses in human and animal immune systems (e.g., animal anti-drug antibody response versus to human ADA). For clinical studies, immunogenicity assessment should always be considered in order to: [1] detect immune reactions, [2] investigate binding and neutralizing ADAs and their interactions; and [3] receive PK-and PD data and data on efficacy and safety.

A risk-based approach should be applied to analyze and mitigate immunogenicity. This includes extension and adaption of pre-approval studies if necessary, as well as consideration of further studies in the post-approval phase to assess rare immunogenicity related events. Similar to the FDA guidance document, the EMA guidance document describes in great detail the clinical consequences of and the immunogenicity influencing patient- and product specific factors. However, in contrast to the FDA guidance document it does not provide any recommendations to address the patient- and product specific factors that affect immunogenicity. Also in contrast to the structure of the FDA guidance document, the EMA guidance document discusses the non-clinical immunogenicity testing in a separate section and recommends the application of emerging technologies such as novel *in-vivo, in-vitro* and *in-silico* models to estimate potentials of risk for immunogenicity. [61]

Clinical and non-clinical comparative immunogenicity testing should be performed with biosimilar products derived from the commercial manufacturing process. Blood samples should be taken and banked for future testing. The EMA guidance document provides further detailed information to the immunogenicity assessment testing strategy and development of assays for detecting and measuring clinically relevant immune reactions such as: [1] screening assays; [2] assays that confirm the presence of antibodies; [3] neutralization assays; and [4] assays for comparative immunogenicity. [61] All assays are expected to be fully validated for marketing authorization purpose as discussed in the mentioned EMA guidance document.

For immunogenicity testing, patients should be studied using routine repetitive sampling as well as unscheduled sampling that depends on the symptoms in case of undesired immune reactions. It is recommended to always collect baseline samples. [61]

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[61] Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins; EMEA/CHMP/BMWP/14327/2006 Rev1; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/10/WC500194507.pdf

The sampling plan should be designed in a way to separate patients that develop antibodies on a temporarily basis from patients that develop anti-drug antibodies on a permanent basis. The length of post-treatment follow-up sampling should be of adequate time duration to provide information on the persistence of the immune reactions and to detect any suppressed reactions; it should be taken at the earliest upon four weeks after the last dose was administered. [61]

The EMA document recommends more frequent sampling during the initial phase of drug administration with a reduced sampling frequency for long-term (e.g., chronically administered products) use. For chronically administered products, a follow-up period of at least one year is recommended; however, if properly justified, a shorter follow-up period is possible. As the development of non-neutralizing antibodies may impact pharmacokinetic behavior of the product (e.g., in the elimination phase by increasing efficacy due to lengthen the half-life), it is recommended to collect PK- data along with the immunogenicity data during repeat dose studies to enable the early detection of changes in the PK. The studied target population should be sensitive enough to detect any clinically relevant differences in immunogenicity, and should be compiled of subjects that have not been previously exposed to the (reference-) product but for whom the product is indicated. [61] The discussed EMA guidance document does not address extrapolation of immunogenicity data whereas the FDA counterpart guidance document does.

The EMA guidance document on immunogenicity assessment indicates that the influence of leachables to immunogenicity (e.g., substances or particles leached-out from rubber stoppers or syringes of the container closure or drug delivery device) should be considered. [61] It also indicates that considerations should be given to substances or particles leached-out during clinical application (e.g., infusion devices or accessories) practice. However, leachables are neither explicitly mentioned, nor is any data or testing requirements specified in that or in any other relevant EMA guidance document for biosimilar products.

Specifics in immunogenicity assessment of monoclonal antibodies

The EMA guidance document *"Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use"* addresses specific immunogenicity related issues experienced with mAbs. [204] It recommends a risk-based approach in the evaluation and mitigation of immunogenicity and provides risk management information. The guidance document amends the information provided in the main EMA guidance document on immunogenicity assessment discussed before, by discussing difficulties when using screening and confirmatory assays, measuring neutralizing capacity of antibodies induced against mAbs, and provides information to the risk management of immunogenicity. [61]

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[61] Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins; EMEA/CHMP/BMWP/14327/2006 Rev1; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/10/WC500194507.pdf

[204] Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use; EMA/CHMP/BMWP/86289/2010; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128688.pdf

In contrast to other therapeutic proteins, it is unlikely that antibodies developed against therapeutic monoclonal antibodies will induce cross-reactions and neutralizing endogenous counterparts (e.g., such with erythropoietin (EPO)). Monoclonal antibodies are often considered as alternative therapies and typically not used as replacement therapies. The mAb specific EMA guidance document on the immunogenicity assessment of monoclonal provides specific advice to antibody detection screening assays, and recommends the use of alternative approaches to that used for other therapeutic proteins. [204] These recommended approaches work without anti-immunoglobulin reagents (e.g., use of a bridging design for Enzyme-linked immunosorbent assays (ELISAs) or electrochemiluminescence (ECL) assays; or use of surface plasmon resonance (SPR) procedure). Anti-immunoglobulin reagents cannot be used in mAb antibody detection as they typically bind to the mAb itself. However, the alternative approaches may be less sensitive than methods more commonly used. The guidance document also discusses the issue of the presence of mAbs in samples intended to be analyzed. Here, the relatively high half-life of mAbs may complicate the identification of antibody responses in samples. To solve this issue, the sampling may be timely delayed or the use of specific ECL based immunoassays that contain a preparatory antigen-antibody dissociation step may be used. [204] Regarding the selection of a positive control serum, which is considered important to control sensitivity and specificity of the assay, the use of human sera should be preferred. Sera from non-human primates and / or the use of an antiidiotypic antisera or mAb may be alternatives to human sera. Antiidiotypic means an antibody that binds with the variable region of another antibody, the idiotype. Spiking samples may be used in verifying assay specificity. [204]

The clinical effect that a monoclonal antibody generates can be a summary of various mechanisms a mAb uses in combination and in a cumulative or synergistic way. If so, the assessment of the neutralizing potential is more difficult and should start with rigorous characterization of the biological properties of the mAb in order to determine a suitable assay strategy. Overall, competitive ligand binding assays to assess neutralization capacity are recommended.

The following items should be taken into account for risk identification when developing the immunogenicity related risk management for mAbs: [1] available and unavailable experience to related mAbs (e.g., similar to target class, same expression system); [2] mAb structure (e.g., mAb sequences (heterologous, humanized, human), glycosylation patterns, production impurities, mode of action (e.g., cytolytic, apoptotic) and character of the target molecule (e.g., immune suppressing, immune stimulating); [3] clinical considerations (e.g., unwanted immune responses and influencing factors). [204]

During the risk assessment, all identified risks should be assessed within a multidisciplinary approach and risks should refer to the relevant comparability testing. The overall risk assessment should enable applicants to provide information relating to the severity, rate of occurrence and detectability of the risks. The conduct of further postmarketing -surveillance, -monitoring or -studies should be considered.

[204] Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use; EMA/CHMP/BMWP/86289/2010; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128688.pdf

For risk monitoring purpose, the guideline is very similar to the relevant FDA guidance in content. The EMA document requires frequent sampling during all phases of development for mAbs with higher risks, but allows a reduced sampling frequency for low risk mAbs in later phases of development. In addition, and similar to the FDA guidance document, it recommends a real time analysis of samples and the simultaneous collection of data regarding the antibody level, PK-/PD-parameters as well as efficacy and safety data in case of repeated administration for high-risk mAbs. [204]

14.6 Overall summary of clinical safety requirements

The following text summarizes the most significant items mentioned above and outlines the identified differences between the scientific recommendations for the clinical requirements of the two regions.

A stepwise approach is generally recommended from both regulatory authorities for conducting clinical testing. Regarding the testing program, the testing steps and their order are the same in both regions. The testing program begins with PK- / PD-studies including immunogenicity, followed by efficacy and safety studies and, if necessary, confirmatory PK- / PD- trials. The evaluation approach for clinical data is the same as that for non-clinical data; the totality of comparability data must demonstrate biosimilarity between the compared products. Comparative PK- studies that ideally include PD- studies and immunogenicity testing are considered essential in both regions to establish biosimilarity. Further, both regions agree that such studies should be conducted in a parallel group design for products with a long half-life, and in cross-over design for products with short half-life. The relevant FDA scientific considerations guidance provides more detailed information to the definition of short half-life and long half-life. [160] Both regions require that the selected PK- parameters should be pre-defined and their limits scientifically justified. The same recommendation is given for the choice of PD-markers; these should depend on their ability to demonstrate the intended clinical outcome. Both authorities, the EMA and the FDA, provide the possibility to skip comparative efficacy studies (USA) or confirmatory clinical trials (EEA).

In contrast to the EMA requirements, the FDA allows in certain cases (e.g., product can only be administered to patients) the possibility of the selection of an alternative dosing scheme if the appropriateness is scientifically justified.

Both authorities consider immunogenicity studies as a key element in biosimilarity demonstration, and both authorities recommend a risk-based approach. Both regions recommend that a study utilizing a comparative parallel-group design (e.g., a head – to - head study) be conducted in a sensitive population that have not been exposed to the (reference-) product previously but for whom the product is indicated. Further, both regions recommend a follow-up period of at least one year for chronically administered products although the EMA allows shorter periods (e.g., 6

[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

month) if the rationale is well documented. Both authorities recognize that the length of the follow-up periods for other, non-chronically administered products depends on several factors. The FDA expects the sponsors to proactively define the clinical immune response criteria (e.g., definition of significant clinical incidents) for each type of potential immune reaction. Both authorities recommend sampling be conducted more frequently during the initial phase of drug administration while less frequent sampling is recommended for long-term use (e.g., chronically administered products). The duration of repeat sampling periods should be sufficient enough to determine the type of immune reaction (e.g., persistent, neutralizing, or linked with clinical long-term complications). Both authorities recommend a real-time-assessment of samples in certain situations (e.g., high risk situations). The EMA´s mAb specific guidance document recommends a reduced sampling frequency for low risk mAbs in later phases of development but requires more frequent sampling during all phases of development for higher-risk mAbs. No mAb related information is provided by the FDA as no mAb specific guidance exists.

For comparative clinical studies, both regions recommend a randomized equivalence parallel group trial design to be conducted in models sensitive and sufficiently sized to identify safety- and efficacy related discrepancies respectively to detect clinically meaningful differences. While the FDA recommends symmetric inferiority and superiority margins to establish the necessary statistical evidence, the EMA simply refers to the ICH E9 guideline and the EMA guidance document *"Guideline on the choice of the non-inferiority margin"* in which non-inferiority margins are discussed and recommends comparable margins to be statistically and clinically pre-specified and justified by using the reference product data. [240] Generally and in both regions, the population size studied should be sufficient to detect clinically meaningful differences in safety and efficacy between the two compared products.

In both regions, biosimilar products derived from the commercial manufacturing process should be used to generate clinical trial data. In addition, assays used to generate clinical trial data should be fully validated.

Both regions allow the possibility to extrapolate safety, efficacy and immunogenicity data to other indications / conditions of use. To do this, the EMA requires a scientific justification and, in certain cases, additional data. [57] For mAbs the EMA requires additional data for each additional sought indication, if the essential data that demonstrate comparability are based on pharmacodynamic study data and for the indications sought different mechanisms of action or uncertainty exist. [200]

In contrast, the FDA only requires that there is a scientific justification for each additional indication that is sought. The FDA also recommends studying a condition

[240] Guideline on the choice of the Non-Inferiority Margin, Doc. Ref. EMEA/CPMP/EWP/2158/99; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003636.pdf

[57] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev1, 18 December 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf

[200] Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues; EMA/CHMP/BMWP/403543/2010; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

of use sensitive enough to detect clinically meaningful differences between the compared products. [215]

By regulation, the EEA does not require that biosimilarity demonstration to the reference product be repeated when changes are made to the manufacturing process of the biosimilar product after the proposed product has received marketing authorization. [30] The FDA guidance documents provide no information to this topic.

For changes in the manufacturing process of biological products, the EMA document *"Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process - non-clinical and clinical issues"* provides information on non-clinical and clinical testing and defines on the basis of time points the extent of clinical studies. [241] A risk-based approach is used to determine the need and extent of non-clinical and clinical studies. There is no newly released FDA guidance that addresses this topic; however, the FDA document *"Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology Products"* from 1996*;* and the FDA scientific considerations guidance document refer to the ICH guideline document Q5E *"Comparability of biotechnological/biological products subject to changes in their manufacturing process".* [242] [160]

Overall both regions regulations are very similar as the same topics are covered by the relevant guidance documents. However, unlike the EMA, the FDA does not provide any specific guidance on mAbs. No fundamental differences were identified between the two regions which may impact the safety of biosimilar products. However, although the extrapolation of clinical safety, efficacy and immunogenicity data is possible in both regions, the extrapolation topic is handled differently and may influence the safety of biosimilar products in the USA due to the lack of the additional data requirement when extrapolating data.

14.7 Analysis of the quality considerations

Both regulatory regions have issued a scientific document discussing product comparability under a quality point of view. These documents are the EMA similar

[215] Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, April 2015, Guidance for Industry; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

[30] Guideline on similar biological medicinal products; CHMP/437/04 Rev 1, 23 October 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

[241] Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process - non-clinical and clinical issues; EMEA/CHMP/BMWP/101695/2006; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003935.pdf

[242] Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products; April 1996, last update: July 6, 2005; http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm

[160] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

products – quality issues guidance document and the FDA´ quality considerations guidance document and these will be compared in this section. [199] [159]

USA

Because quality attributes may be used when designing the comparability program, comparative analytical and similarity data should be available at early stage of development and should be submitted to the FDA, ideally: [1] pre-IND; [2] together with the IND-submission; or [3] when providing data from initial clinical studies (e.g., PK/PD testing). [159] In general, the FDA recommends the use of state-of-the-art technologies, assays and orthogonal methods which should include knowledge about their limitations. For analytical studies, an appropriate quantity of multiple lots of the reference product as well as the proposed biosimilar product should be used to determine the variability within product lots (product consistency). Also to facilitate the setting of product consistency acceptance criteria, it is recommended that lots used in analytical similarity studies should be identifiable and lot expiration dates should be documented along with the testing time point and time point when the lots were used in other studies. [159]

Within the comparative physicochemical and functional testing, quality attributes should be set in order to identify and quantify the product in order to define its safety, purity, and potency. The structure (e.g., heterogeneity) and function of a biological product may be influenced by a number of circumstances, such as protein modifications (e.g., posttranslational, deliberate) during cell culture, during manufacturing processes and/or during product storage.

When the analytical characterization has observed qualitative or quantitative differences in product quality attributes, these may be further assessed using a fingerprint-like analysis that is eligible to analyze numerous products attributes. [159]

Important factors that should be considered in the comparability program include:

1. Type of expression system
   The type of expression system that is used for the biosimilar product may vary (e.g., in host cell and expression construct) which may impact the process- and product-related substances, impurities, and contaminants or may lead to any protein modifications. Therefore, any differences between the expression systems should be kept to a minimum; [159]
2. Manufacturing processes
   The manufacturing processes should be consistent, well controlled and run under a quality- and risk-management. If changes to the manufacturing

[199] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1); EMA/CHMP/BWP/247713/2012, Rev.1; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167838.pdf

[159] Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf

[159] Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf

process occur after analytical testing or clinical studies, the pre- and post-change comparability of the biosimilar product should be demonstrated. This may require additional analytical testing depending on the extent and nature of the process change; [159]

3. Physicochemical properties
   The testing applied to assess the physicochemical properties of the products should be sensitive and specific enough to provide significant data in order to demonstrate biosimilarity and to detect potential differences in quality attributes of the compared products; [159]

4. Functional assays
   Potential assay limitations should be considered as well as the limited appropriateness of in-vitro bioactivity assays; [159]

5. Receptor binding and immunochemical properties
   Receptor binding and immunochemical properties of the biosimilar product should be analyzed when these characteristics are part of the activity of the biosimilar product. Different analytical test methods are available to investigate the kinetics and thermodynamics of binding and results may provide additional information to the higher order structure and functional activity of the biosimilar product; [159]

6. Impurities
   The FDA recognizes that process-related impurities (e.g., resulting from cell-substrates) vary between manufacturing processes. However; if differences in the impurity profiles of the compared products are observed, they should be assessed side-by side in a risk-based manner. The differences and the potential impact to the product safety should be discussed and supported with relevant data. Analytical procedures used should be validated and eligible for identification, detection and quantification of impurities. Furthermore, critical raw materials should be reviewed; and virus removal / inactivation as part of the manufacturing process should be tested and confirmed; [159]

7. Reference product and reference standards
   The FDA recommends providing information on the extraction steps in cases where the drug substance has been extracted from the reference product for analytical similarity testing purpose. Also, information on the impact of the extraction to the quality attributes should be included. Publicly available, well-established reference standards for the protein (e.g., international standard for calibration of potency) should be used in the physicochemical and/or functional testing. However, the use of reference standards does not make product-individual comparative testing unnecessary in the demonstration of biosimilarity and does not replace the reference product. [159] A qualified in-house reference standard should be used in manufacturing- and product control (see ICH Q6B);

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[159] Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf

8. Finished drug product testing

   Finished drug product testing should be performed on a bulk drug substance. [243] Ideally sponsors should use the finished drug product for analysis; however, if particular quality attributes are detected more efficiently in the drug substance by a certain analytical method and in case these attributes are critical in the products manufacturing, both, the drug substance and the finished drug product should be characterized in a comparative manner. In case where different excipients than the reference product it uses are processed, these should be identified and toxicology data should be provided. Also, when the product formulation or the primary packaging (container closure) deviates from that of the reference product (e.g., reformulation), this may affect the approach to the subsequent clinical testing (e.g., selective and targeted or any other) and additional testing may be necessary to minimize safety and efficacy related concerns to the biosimilar product; [159]

9. Stability testing

   Stability testing should be comparative in nature and should comprise accelerated and stress testing, including forced degradation studies. Testing should be performed under multiple stress conditions such as high temperature, freeze / thaw, light exposure, and agitation. The proposed shelf life of the biosimilar product should be facilitated with real time data and real condition stability data of the biosimilar product. [159]

<u>EEA</u>

A continuous manufacturing process is considered a key element in biotechnology-derived products production. The manufacturing process defines the molecular characteristics of the active substance and process- and product-related substances and impurities as well as modifications to and variants in protein structures in the biological product. A quality target product profile (QTPP) specific for the proposed biosimilar product should be pre-defined which serves as the basis for the product – and manufacturing process development. When selecting the expression system any impacts to the protein (e.g., changes in protein structures or impurity profile, etc.,) should be considered.

It is not necessary that the formulation and / or container closure system of the proposed biosimilar product is the same as that of the reference product. When differences exist, the impact to the products safety and efficacy should be properly justified. In all cases, it should be demonstrated that the chosen formulation is stable to environmental and any other influences. Further, it should be demonstrated that the product formulation is compatible with excipients, packaging materials, diluents

[243] 21 CFR 207.3(a)(4), April 2016; https://www.gpo.gov/fdsys/pkg/CFR-2016-title21-vol4/pdf/CFR-2016-title21-vol4.pdf

[159] Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; Guidance for Industry, April 2015; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf

and a proper stability, integrity, activity and strength of the active substance should be shown. [199]

Any changes to the manufacturing process should be assessed in accordance to ICH Q5E and described in the application dossier. In order to develop comparable quality, safety and efficacy data to establish biosimilarity to the reference product, it is always advisable to use a biosimilar product produced with commercial manufacturing process conditions.

The ICH Q5C should be consulted for stability testing. The extrapolation of stability data from the reference product is not possible; therefore, additional supportive data shall be provided.

It should be noted that once a biosimilar product has received marketing approval, regulations do not require a re-demonstration of biosimilarity. [199] This is also stated in the EMA´ similar products guidance document; however, neither the regulations nor the guidelines discuss or justify the rationale. [30]

Besides manufacturing relevant factors, there are other important quality factors that should be considered in the comparability program including:

1. Reference medicinal product comparability
   An appropriate quantity of multiple different batches of the reference product should be used. It is recommended that batches of the reference product used are identifiable (e.g., brand name, formulation, strength, number of batches, lot number, age of batches, etc.); [199]

2. Biosimilar comparability exercise
   Extensive side-by-side comparative studies are recommended to detect differences in quality attributes between the compared products. While the proposed finished product, including its product-related substances, should demonstrate biosimilarity to the reference product, the process-related impurities may vary. However, the process-related impurities should be kept at minimum, ideally through a reliable and efficient purification step in the manufacturing process. If process-related impurities are minimal, a non-clinical testing program to qualify the process-related impurities may be unnecessary. If possible, quantitative ranges for quality attributes should be established for biosimilar comparability purpose. The quantitative ranges should be based on the measured ranges for quality attributes from the reference product, and the variability range of the reference batches should not exceed that of the reference product. Such established ranges in quality profile may be helpful in assessing the impact of manufacturing process changes to the biosimilar product in order to support comparability

[199] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; EMA/CHMP/BWP/247713/2012, Rev.1; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

[30] Guideline on similar biological medicinal products; CHMP/437/04 Rev 1, 23 October 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

[199] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; EMA/CHMP/BWP/247713/2012, Rev.1; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

demonstration. Where quality attributes measures (pre-change versus post-change) are out of the specified quality attribute ranges this should be justified with respect to its influence on product safety and efficacy; [199]

3. Analytical considerations

For analytical considerations, the EMA recommends the adequate qualification of methods (regarding their intended purpose) used in comparability testing. This is especially important for the methods used to determine product characterization. Further, the EMA indicates, that the applicant is in charge of ensuring the adequacy of the selected methods. Publicly available standards and reference materials such from Ph. Eur. should be applied in order to qualify and standardize the methods used. However, like the FDA quality guidance, the EMA considers publicly available standards such as the Ph. Eur. as inadequate for comparability demonstration purpose. Therefore, they cannot replace the reference product. Instead, the EMA recommends extensive comparability testing with state-of-the-art technologies; assays and sensitive orthogonal methods; including knowledge about their limitations. In cases where analytical testing samples were extracted or otherwise processed to enable their use in certain analytical techniques, these procedures should be described, and it should be discussed if and how the used procedure could influence the test samples; [199]

3.1. Physicochemical characteristics

In the comparison of the physicochemical properties physical and chemical characteristics (e.g., texture, physical properties, primary and higher order structures of the protein product) will be evaluated and the structure of product-related substances and impurities will be identified using appropriate analytical test methods. If glycosylation structures or variants are found in the biosimilar product which were not detected in the reference product these should be justified with respect to non-human structures (e.g., linkages, sequences or sugars). [199]

3.2. Biological properties

In order to study the biological properties, biological assays should be used under consideration of their limitations. The assay outcomes should be calibrated against an international or national reference standard; [199]

3.3. Immunochemical characteristics

With respect to the immunochemical characteristics the EMA guideline states that immunological functions of monoclonal antibodies and related substances should be compared including the assessment of the affinity of the two products to the desired target as well as the binding affinity of the fragment crystallizable

[199] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; EMA/CHMP/BWP/247713/2012, Rev.1; ; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

(Fc) to relevant receptors. [199] The guidance document refers to the similar products mAb guidance document.

3.4. The purity / impurity profiles
The purity and impurity profiles should be studied in a quantitative and qualitative manner and compared to the results of the comparator product. Identified impurities should be documented and properly justified with regard to their potential risks (e.g., inducing of immune reactions). The qualitative comparison of product-related impurities is considered unnecessary as they vary between processes; [199]

3.5. Quantity
A suitable assay should be used to establish product quantity and it should be confirmed that the strength of the biosimilar product is similar to that of the reference product. To express the quantity of the biosimilar product the same units should be used as used for the reference product. [199]

4. Specifications
Regarding to the product specifications the EMA guideline references ICH Q6B and states that the proposed shelf life of the biosimilar product should be supported with full stability data of the biosimilar product whilst comparative real-time and real-condition stability studies between the compared products are not considered necessary. [199]

14.8 Overall summary to safety relevant quality considerations

The following text summarizes the most significant items mentioned above and outlines the identified differences between the scientific recommendations regarding the quality considerations of the two regions.

The FDA´s quality considerations document focuses on CMC related information that should be considered in the comparability program and be described in the CMC section of the drug dossier. Like other topics related to drug approval, the FDA encourages applicants to discuss any CMC related questions with the FDA from the beginning of the development process. The less voluminous and comprehensive EMA quality considerations guidance document focuses on quality requirements for a proposed biosimilar product and addresses similar issues as the FDA document, although not in such a great detail. However, the grade of regulation is very similar as the same topics are covered by the relevant guidance documents.

Due to the different regulatory approach regarding drug development and -application as well as approval, the FDA recommends submitting comparative and similarity data at an early stage of development; ideally pre-IND. This is not in with the EMA. The EMA provides the possibility to request scientific advice, but does not

[199] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; EMA/CHMP/BWP/247713/2012, Rev.1; ; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

encourage the applicant to provide data at an early stage. The review and approval process in the EEA region starts with the submission of the application dossier.

The requirements regarding process-related impurities differ slightly. Although the FDA recognizes that process-related impurities vary between manufacturing processes, differences in impurity profiles of the reference product and the proposed biosimilar product should be assessed, compared and supported by data in order to determine the potential impact to safety and efficacy. In contrast, the EMA guidance document only requires documenting and properly justifying identified impurities with regard to their potential risks (e.g., inducing of immune reactions).

Furthermore, while the EMA requires keeping process-related impurities as low as possible by applying an efficient and reliable purification step, the FDA recommends the testing and confirmation of removing / inactivation of viruses within the manufacturing process.

A slight difference compared to the EMA requirements concerns finished biosimilar product formulations and / or container closure systems (primary packaging) that are different to that of the reference product. In such a case, additional data may be required by the FDA to sufficiently rationalize why the deviation does not affect the safety and efficacy of the biosimilar product. With the EMA, the use of a different formulation and / or container closure system is also allowed. In such cases and along with the common requirements to formulation testing, the impact of the different formulation and / or container closure system to the products safety and efficacy should be properly justified.

While the FDA guidance document has specific requirements for stability testing, the EMA scientific document has very little information on stability testing and refers to ICH Q5C which states that stability data cannot be extrapolated from the reference product. The FDA guidance document also refers to the ICH Q5C, but the FDA document provides details on required testing such as comparative stability testing should include accelerated and stress testing as well as forced degradation studies; conducted under multiple stress conditions.

In the FDA´ s view, real-time data and real-condition stability data should support the proposed shelf life of the biosimilar product. Similarly, the EMA requires that the proposed shelf life of the biosimilar product be supported with full stability data, but notes that comparative real-time, real-condition stability studies between the compared products are considered not necessary. However, both guidance documents (EMA and FDA) refer to the ICH Q6B for specifications.

While the EMA similar products - quality issues guidance document states that the re-demonstration of biosimilarity is not required by regulations once a biosimilar product has received marketing approval, the FDA guidance document does not provide any information in order to address that question.

Overall, the scientific content of the both documents is similar with slight differences that make the FDA document more informative and meaningful; and some requirements are a little tighter. Some of the slight differences could influence the product safety, namely using a different container / closure or delivery device system with no EMA requirements requiring additional testing or data to investigate the potential impact on the efficacy and safety of the biosimilar product as an

appropriate justification is considered as adequate. The impact of the container / closure or delivery device system to the finished product is illustrated with the Ortho Biotech Eprex / Erypo uncoated rubber stopper investigation published in “Kidney International” in 2005. [244] The investigation result supports the hypothesis of the impact of container / closure or delivery device system to the drug safety. The investigation showed that patients with chronic kidney disease treated with Eprex® epoetins by subcutaneous administration had an increased incidence of pure red cell aplasia (PRCA) caused by leachates from uncoated rubber syringe stoppers.

Appendix M provides a tabular overview of found similarities and differences between regulatory and scientific requirements in the EEA and the USA.

[244] The increased incidence of pure red cell aplasia with an Eprex; KATIA BOVEN, Available online 9 November 2015, http://ac.els-cdn.com/S0085253815507242/1-s2.0-S0085253815507242-main.pdf?_tid=31043132-6e84-11e6-bd72-00000aacb362&acdnat=1472542651_e55754230603c365440a4ff75c5ab801

15 Improvement potential and suggestions

On the basis of the EMA-and FDA guidance documents, some potentials for improvement were identified that may help improve the safety of biosimilar products.

15.1 Improvement potential in the European Union and USA

The largest potential for improvement is related to the overall safety-relevant regulatory requirements. The most significant suggestions for improvements for both regions are listed and explained below.

1. Use of a non-EU or non-US licensed reference product
   When using different reference products (e.g., EU reference product and non-EU reference product) the generated bridging data may raise the risk of potential bias regarding safety data.
   Suggestions:
   - Eliminate the possibility of using a non-EU or non-US reference product; or
   - Restrict and clearly define the type of studies where the use of a non-EU- or non-US reference product is allowed, and
   - Provide regulatory guidance and define quality requirements for statistical evaluation of comparative assessments in order to avoid errors e.g., within the empirical data collection (probably sampling) which may cause potential bias e.g., systematic biased error, or random sampling error
2. Automatic substitution
   The individual US-states allow automatic substitution of biological products with interchangeable biosimilar products, providing they have passed the biosimilars legislation with or without additional requirements e.g., patient and / or physician notification, regarding to the automatic substitution.
   In the EU, some member states allow automatic substitution by national law and other does not. The approach in both regions (USA and EU) regarding to the automatic substitution may hinder postmarketing surveillance activities.
   Further, immunogenicity may be triggered when biological products are switched back and forth with the interchangeable biosimilar product. Consequences of antidrug-antibody-development could be the loss of drug efficacy or serious adverse events which poses a safety risk to patients.
   Suggestions:
   - Harmonize legislation to ensure uniform requirements for automatic substitution
     - EU: Establish requirements for automatic substitution in the EU legislation (Regulation (EC) No 726/2004)
     - USA: Harmonize individual state provisions on automatic substitution restrictions

    - Both: Establish basic requirements regarding information obligations to patients and physicians when a biological product is substituted and regarding prescription information requirements
- Establish regulations to implement a globally working uniform and reliable traceability and identification system to ease postmarket surveillance activities
- In order to avoid immune related consequences, multiple switching back and forth between biosimilar products and biological products should be restricted by legislation (e.g., substitution only allowed when sufficient clinical data are available, automatic substitution not allowed at pharmacy level)
- Switching and multiple switching should only be allowed when suffient switching study data are available for each indication
- Switching studies should become a mandatory part of the approval process of an interchangeable biosimilar product
- In order to gather postmarketing safety and efficacy data, post-authorization studies (PASS / PAES) should become a mandatory post-authorization requirement for biosimilar and interchangeable biosimilar products
- Patient should always be involved in the decision when an interchangeable biosimilar product is intended to be used instead of the biological innovator product because any safety risk regarding the substituted product is with the patient

3. Labeling and naming and prescription information
   Inconsistencies and lacks in labeling and naming as well as to the requirements regarding prescription information may hinder postmarketing surveillance activities through identification and transparency issues and may lead to prescription errors
   Suggestions:
   - Both regions should use the same labeling and naming convention for biological products, biosimilar and interchangeable biosimilar products to facilitate global postmarketing surveillance activities
   - Biosimilar products should be clearly identified as such to avoid prescription mix-ups with biological products
   - Interchangeable biosimilar product should be clearly identified as such to avoid prescription mix-ups
   - The indications for which a substitution of products can take place should be clearly stated on the outer packaging together with the name of the interchangeable product
4. Pediatric assessment
   While the pediatric assessment is not required for biosimilar products in the EU, it is required for biosimilar products in the USA but not for biosimilar products for which an interchangeable status is applied.
   Suggestions:
   - Due to the specifics of biotechnology-derived products (e.g., protein instability, structural modifications, and immunogenic behaviour)

compared to chemically-synthesized drugs, pediatric assessment should always be required in the approval process of biosimilar products and interchangeable biosimilar product in both regions.

Some potential for improvement is related to the clinical safety requirements. The most significant suggestions for improvements for both regions are listed and explained below.

1. Extrapolation of data across indications
   Both regions allow extrapolating safety, efficacy and immunogenicity data across indications when justified. Studying only one indication may not provide adequate data to assess and adopt the potential for safety and efficacy issues including immunogenic risks for several indications.
   Suggestions:
   - Tighten the requirements to always require clinical safety-, immunogenity- and efficacy study data for each indication that is sought independent from previous study or testing results in order to demonstrate biosimilarity to the reference product; or
   - Eliminate the possibility of extrapolating data across indications for biosimilar products.

2. Skipping of studies and conduct of post-authorization studies
   Both regions provide the possibility of waiving confirmatory clinical trials when the data generated in the non-clinical testing and human PK- /PD- studies are sufficient to demonstrate biosimilary comparability. Negative side effects may stay undetected if such study is waived. Further, product superiority may also stay undetected. The conduct of confirmatory trials as well as the extent and size of such study is based on the results derived in non-clinical testing and human PK-/PD- studies. Rare side effects may stay undetected in the pre-approval phase due to a small extent and size of such study. In consequence, such data need to be gathered postmarketing. Though, both regions recommend considering PASS / PAES requirements, but currently such studies are requested for biosimilar products only on a case-by case basis.
   Suggestions:
   - Eliminate the possibility to waive confirmatory clinical trials;
   - The study size should not depend on previous non-clinical study and human PK- /PD- study results.
   - A minimum study size should be predefined by regulation and this size should be met unless properly reasoned (e.g., orphan disease);
   - In order to gather postmarketing safety and efficacy data post-authorization studies (PASS / PAES) should become a mandatory post-authorization requirement for biosimilar products and interchangeable biosimilar products.

Some potential for improvement is related to the quality safety requirements. The most significant suggestions for improvements for both regions are listed and explained below.

1. The re-demonstration of biosimilarity after marketing approval and changes to the manufacturing process is not required

Both regions do not address the re-demonstration of biosimilarity once a biosimilar product has received marketing approval. However, as there is a potential safety risk to the patient, especially when an interchangeable biosimilar product is used as substitute and is switched back and forth, this should be addressed. If changes to the manufacturing process of the (interchangeable) biosimilar product occur, it may happen that the characteristics of the biosimilar product including its safety profile are changed. Thus, it might be possible that after the manufacturing change the biosimilar product is less biosimilar to its reference products than it was before the process change and as demonstrated by the biosimilarity data in the application dossier. Hence, the biosimilar definition would not be applicable anymore for the changed biosimilar product and it cannot be guaranteed that the product that was interchangeable and / or biosimilar before still has this status fully after the change.
Suggestions:

- Regulatory authorities should discuss this topic
- EU and US- legislation and regulations should be modified accordingly to address the issue;
- Scientific guidance documents should be provided to implement requirements for re-demonstration after marketing approval when changes to the manufacturing process occur.

No potential for improvement was found for the non-clinical safety requirements.

15.2 Improvement potential in the European Union

Some potentials for improvement were identified that may help improve the safety of biosimilar products in the EU. The most significant potential for improvement is related to the overall safety-relevant regulatory requirements. The suggestions for improvements are listed and explained below.

1. Determination of interchangeability
   Currently, there is no legislation and regulatory process to determine the interchangeability of biosimilar products on EU-level and the EMA is not responsible and authorized to address this topic. In consequence, determination of the interchangeability is made on national level and is therefore based on different qualitative and quantitative assessment and determination criteria. This approach may hinder global postmarketing surveillance activities, may impact patient safety due to different determination criteria and may influence drug availability in the different EU-member states.
   Suggestions:
   - To allow a uniform and competent authority decision on product interchangeability, the current decentralized (national) approach should be replaced by a centralized European approach by modifying the relevant EU- legislation Regulation (EC) No. 726/2004/EC;
   - The term interchangeability should be defined
   - Uniform and equal standards of determination and criteria to assess the interchangeability should be established in the EU legislation;

- The EMA should become the only authority allowed to assess and determine the interchangeability of biosimilar product using a uniform and centralized process and as part of the marketing authorization process similar to that of the FDA in the USA.
- The EPAR should contain information to the interchangeability of a biosimilar product

2. Requirements to the container closure system and delivery device
   The EMA similar products – quality issues guidance document provides the possibility to use a different container closure system as the reference medicinal product uses; provided that its potential impact on the biosimilar product safety and efficacy is appropriately justified. [199] However, the EMA guidance document does not further detail this topic, neither for biosimilar mAb products nor for biosimilar product at all.

   In contrast, the FDA is aware of the safety risks (e.g., immunogenicity) and quality issues appearing from interactions between biotechnology-derived product and container closure or delivery device systems. The FDA´s immunogenicity assessment guidance document recommends maintaining detailed raw material data of the container closure system and further recommends performing an extensive extractables and leachables laboratory assessment in order to evaluate the attributes of the system and possible interactions that could lead to degradation of the product structures. [60].

   Suggestions:
   - Tighten the requirements for the use of a different container closure system and/or delivery device similar to the FDA requirements. This includes defining justification requirements and testing requirements for extractables / leachables;
   - Assess these data over shelf life duration;
   - The topic should be more detailed in the relevant EMA guidance document on quality issues
   - Requirements to the container closure system and delivery device

3. Drug shortage pre-notification requirement
   While the FDA requires a notification of six month prior to a discontinuance or interruption in product manufacturing that could cause a significant disruption of drug product availability, a notification of only two month is required within the EU and only if the product ceases to be made available on the market (temporarily or permanently). This may lead to drug unavailability and could impact patient safety.
   Suggestions:
   - Extent the time frame of the pre-notification requirement from two month to six month.

[199] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; EMA/CHMP/BWP/247713/2012, Rev.1; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

[60] Immunogenicity Assessment for Therapeutic Protein Products; Guidance for Industry; April 2014; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf

4. Protection periods
   While the protection period for the biological innovator product is 12 years in the USA it is typically 10 years in the EU. Biosimilar products are sooner available on the EU- market, but two years postmarketing data of the reference product which would be available with the US-protection period, cannot be included and evaluated in the the approval process of the proposed biosimilar product.
   Suggestions:
   - Extent the protection period of the biological innovator product to 11 years.

5. General approach of the regulatory authorities regarding the process of marketing authorization
   In contrast to the EEA, the generation of clinical data in the USA occurs in the centralized regulatory framework of an investigational new drug application and therefore is an inherent part of the application and review process with the FDA. Thus, the FDA is involved in and familiar with the drug product at a very early stage of drug development. This differs from the process in the EEA where the approval process starts at a later stage with the submission of the dossier. Further, the FDA encourages the applicant to discuss the development program of the proposed biosimilar product and other topics at an early stage and additionally offers five different types of meetings that address topics specifically of biosimilar products while the EMA only offers regular pre-authorization scientific advice meetings.
   Suggestions:
   - The EMA should get involved in the application process at an earlier stage and should more actively encourage applicants to seek advice and meetings with the EMA.
   - The EMA should provide advice meetings that specifically address the topics of biosimilar products.
   - The review, approval and supervision of clinical trials should be centralized with the EMA to involve the EMA in the approval process at an early stage.

15.3 Improvement potential in the USA

There was no significant improvement potential found for the USA other than the items already described above.

16 Conclusion and Outlook

16.1 Conclusion

No major differences between the EU and the USA were identified with respect to the overall regulatory-safety standards that apply for biosimilar products established by the EU- / and US- law and as recommended in the scientific EMA- and FDA guidance documents.

Except of slight differences, the overall safety-related regulatory requirements required by legislation in the EU and the USA are very similar, including pharmacovigilance requirements. The FDA regulations (CFR) require stricter reporting (e.g., reporting of biological product deviations) and processing (e.g., prompt review of adverse events) than that required by the EU and the regulation of drug shortage is different in the two regions. By EU regulation, a minimum of one qualified person to perform certain safety-related tasks (e.g., batch compliance), the FDA does not require that position. Further, the EU legislation has established and implemented the black triangle labeling that represents extended monitoring of new and high-risk products; a comparable instrument is not implemented yet in the USA. While the US- law considers the determination of interchangeability this is not part of the EU legislation. And the law in both regions, the EU and USA, does not consider the re-demonstration of biosimilarity after a change to the manufacturing process occurs post-authorization.

While the US-law provides the FDA with more authority and power than the EMA is provided by Regulation (EC) No. 726/2004, the regulatory requirements established by EU legislation provide the manufacturers with more individual responsibility (e.g., they are responsible to watch their distributors) than the US-law provides to the US-American medicinal product manufacturers. The main European legal document for medicinal products, Directive 2001/83/EC needs to be transposed into national law by the EU-member states while the United States Code applies without transposing into national law. In consequence, the EU-member states have more freedom regarding the implementation of the EU Directive into their national law.

Regarding the pharmacovigilance and postmarketing requirements in both regions, the EU and the USA, these are very similar for the last few years. In both regions, pharmacovigilance includes postmarketing studies, clinical trials, risk evaluation and risk mitigation strategies, patient registries and special labeling. Although appropriate instruments to monitor and further confirm the safety and efficacy of medicinal drug products are available (e.g., postmarketing studies), their application is handled differently and on a case by case basis.

Regarding the regulatory burden and available scientific guidance documents, there are some differences between the EU and the USA. The regulatory burden in the EU is higher than in the USA due to the European and national legislations and the required transformation of EU legislation into national law. The quantity of available guidance documents, in particular documents which address the specifics of individual product classes, is higher in the EU than in the USA. The scientific value, quality and content of the available scientific guidance documents regarding quality

issues, non-clinical and clinical requirements as well as overall safety-related considerations to biosimilar products is high in both regions.

The scientific EMA- and FDA guidance documents concerning the quality, non-clinical and clinical safety requirements for biosimilar products are very similar and comparable. The scientific content of the documents is mostly the same, but there are small differences (e.g., better explanations, examples) that make the FDA documents clearer and more meaningful.

The most significant differences between the two regions, EU and USA, that were identified in the scientific guidance documents and which belong to the safety of biosimilar products are related to the: [1] determination of interchangeability; [2] automatic substitution of biosimilar products; [3] pediatric assessment requirement; [4] the extrapolation of safety and efficacy data including immunogenicity data across indications; and [5] testing requirements when using a different container closure or delivery device system.

16.2 Outlook

Overall, there is a clear trend towards the increasing usage of biosimilar products in both the EU and the USA and it is assumed that the scientific requirements and regulatory approaches to biosimilar products in the EU and the United States are adjusted to each other in the coming decades. It is expected that further scientific guidance documents for biosimilar products will be published from both regulatory authorities with increasing market experience related to those products. In the European Union the topic of product interchangeability must be addressed by legislation and in both regions the re-demonstration of biosimilarity after marketing authorization when changes to the manufacturing process occur.

There are several cooperative projects between the EMA and the FDA for biosimilar products with the aim to harmonize the scientific practice applied to these products in order to minimize regulatory discrepancies and to expedite the availability of biosimilar products to patients. [245] To improve pharmacovigilance, the exchange of relevant important information (e.g., product risk-assessments and related safety issues) and collaboration between regulatory authorities is further developed within the pharmacovigilance cluster that was established in 2014. [246] [247] [245] Further, since the last few years, cooperation is established also in other areas such as inspections (e.g., mutual GMP-manufacturing site inspections), parallel scientific advice and best regulatory approach. [248]

[245] FDA, European Commission and EMA reinforce collaboration to advance medicine development and evaluation, July 2015; http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/07/news_detail_002367.jsp&mid=WC0b01ac058004d5c1

[246] FDA and European Medicines Agency strengthen collaboration in pharmacovigilance area, February 2014; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm386372.htm

[247] Guiding principles for the international pharmacovigilance cluster, May 2015; http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500179390.pdf

[248] General Principles EMEA - FDA Parallel scientific advice, EMEA/24517/2009, http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/11/WC500014868.pdf

To facilitate the new EU-pharmacovigilance package the EMA offers since July 2015 the possibility to obtain scientific advice on post-authorization safety studies (PASS) within a pilot project that specifically addresses non-mandatory PASS-studies. [249] Goal is the establishment of an integrated advice that covers the complete product-lifecycle and which addresses safety-, quality-, and efficacy aspects of medicinal products and facilitates proactive pharmacovigilance strategies. [250] In the USA, meetings with the FDA to discuss such topics and other issues are already common and part of the product approval process. However, this development let assume that the EMA will follow the FDA in their approach and provide advice and meeting options to applicants to get involved in the approval process at an earlier process stage than current.

END OF DOCUMENT

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[251] Martin Brändli , "https://commons.wikimedia.org," Martin Brändli, 08 February 2006. [Online]. Available: https://commons.wikimedia.org/w/index.php?curid=560703 available on https://de.wikipedia.org/wiki/Hybridom-Technik. [Accessed 22 (08:04pm) February 2016].

[252] Hermey, G.; Mahlke, C.; Schwake, M.; Sommer, T., "http://www.springer.com," Spektrum Akademischer Verlag Heidelberg, October 2011. [Online]. Available: http://www.springer.com/cda/content/document/cda_downloaddocument/9783827423689-c2.pdf?SGWID=0-0-45-999954-p174010460. [Accessed 02 (12:55pm) March 2016].

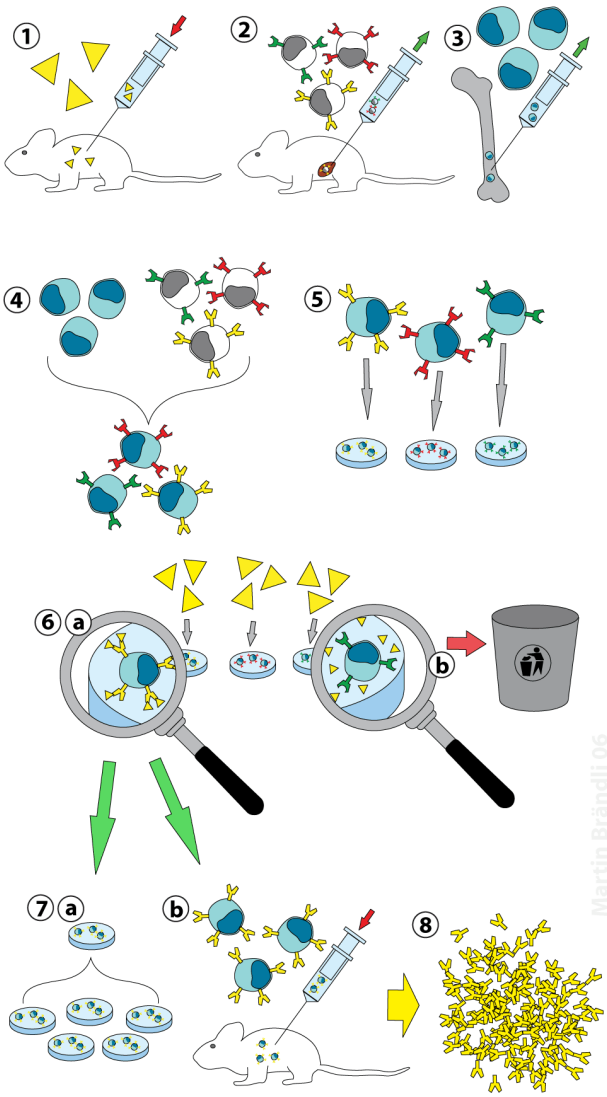
[253] U.S. Government, „http://uscode.house.gov,“ Office of the Law Revision Counsel of the United States House of Representatives, 15 November 2015. [Online]. Available: http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title21-section355c&num=0&edition=prelim. [Zugriff am 16 November 2015; 12:54pm].

[254] European Medicines Agency (CHMP), „http://www.ema.europa.eu,“ European Medicines Agency (CHMP), 30 May 2012. [Online]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf. [Zugriff am 17 November 2015; 03:32pm].

List of Appendices

Appendix A: Schematic diagram of monoclonal antibody production via hybridoma technology

Hybridom – Technik ©by Martin Brändli [251]



(1) Immunization of a mouse; (2) Isolation of B-cells from spleen; (3) Cultivation of myeloma cells; (4) Fusion of B-cell and myeloma cell; (5) Selection and screening of suitable cell lines; (6) Processing or storage of myeloma cells (7) Antibody production in-vitro (7a), or in-vivo (7b); (8) Antibody harvesting [251]

[251] Diagram showing the production of monoclonal antibodies via hybridoma technology, Martin Brändli Eigenes Werk, CC BY-SA 2.5; https://commons.wikimedia.org/w/index.php?curid=560703 available on https://de.wikipedia.org/wiki/Hybridom-Technik

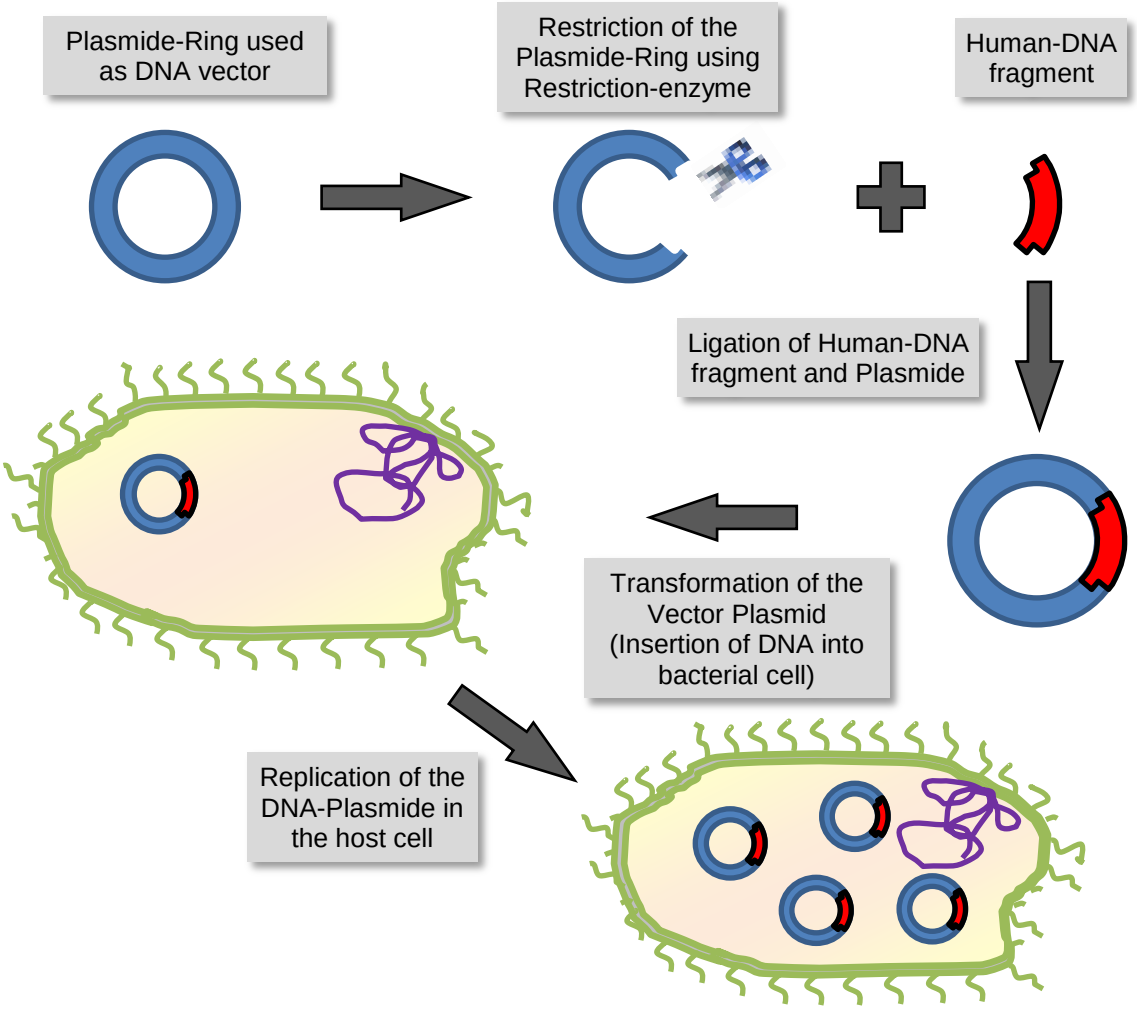
Appendix B: Historic milestones in biotechnological development

Year	Who	Scientific event
6000 years ago	Sumerian	Beer brewing and fermentation
1673	Antonie van Leeuwenhoek	Microscoped bacteria
1864 and 1876	Louis Pasteur	Pasteurization and active immunizations
1882	Robert Koch	Discovered the tuberculosis pathogen
1865	Gregor Mendel	Basics of genetics
1890	von Behring and Kitasato	Use of Antitoxins in infectious diseases treatment
1902	Hans Spemann	Cloned a newt by embryo splitting
1906	Paul Ehrlich	“Magic bullets” concept
1909	Wilhelm Johannsen	Has coined the terms “gen”, “genotype”, “phenotype”
1919	Károly Ereky	Created the term Biotechnology
1928	Alexander Fleming	Discovered mold (fungus) Penicillium chrysogenum producing an antibiotic substance
1944	-	Large scale antibiotics production
1952	Briggs and King	Transfer of frog cell nucleus
1953	Watson and Crick	Discovered double helical structure of the DNS
1975	Köhler and Milstein	Hybridoma-technology to produce monoclonal antidbodies
1977	Genentech, Inc.	Production of human somatostatin in *E. coli*
1980	Exxon	Discovery and patenting on oil absorbing bacteria
1980	Schell	Discovery of Agrobacterium tumefaciens
1982	Genentech	Genetically-engineered Insulin
1982	Frederick Sanger	DNA-sequencing of bacteriophage Lambda
1986	Janssen-Cilag	FDA approval of the first murine Muromonab-CD3 monoclonal antibody Orthoclone OKT3®
1988	Harvard University	OncoMouse
1995	J. Craig Venter	Sequenzierung des Genoms des Bakteriums *Hemophilus influenza*.
1996	Various researchers	DNA-sequencing of *Saccharomyces cerevisae*

Year	Who	Scientific event
1998	James Thomson	Isolation of stem-cells from human embryo and their cultivation
1996	Keith Campbell	Clone sheep Dolly.
1998	Roche	EMA-approval of Rituximab (trade name MabThera®; chimeric anti-CD20-mAb) mAb to treat types of the Non-Hodgkin-Lymphoma
1999	Janssen Biologics B.V.	EMA-approval of TNF-alpha-blocker Infliximab (trade name Remicade®; chimeric mAb) to treat Morbus Crohn and Rheumatoid Arthritis
2000	Roche	EMA-approval of Trastuzumab (Herecptin®) humanized mAb to treat breast cancer and stomach cancer
2003	Human genome project	Sequencing of human DNA
2004	ImClone Systems	EMA-approval of Cetuximab (trade name Erbitux®; chimeric mAb from type IgG1) to treat bowel cancer
2006	Shinya Yamanaka and colleagues	Re-programming of differentiated mouse epithelial cells back into embryonically condition
2009	Fresenius Biotech/ Trion Pharma	EMA-approval of Catumaxomab (trade name Removab) the first trifunctional mAb to treat ascites associated with epithelial cell adhesion molecule (EpCAM) -positive carcinoma

Appendix C: DNA cloning in expression systems

In the following the process of DNA-cloning in order to produce recombinant proteins and recombinant monoclonal antibodies is described in its basics and illustrated with simplyfied figures. Basically, a human DNA-insert, which is a fragment of the human DNA containing the gene desired to get cloned, is placed (cloned) into a DNA-plasmide vector. Typically this is a plasmid ring, annular DNA-molecules of a phage, that is then transformed (into bacterial cells) or transfected (into eukaryotic cells) into a host cell. In the host cell again, the desired human DNA-information contained in the plasmide, is replicated without incorporating the human DNA-information into the host cell genome. Usually, bacterial cells are used as expression systems (e.g., E. coli). [252] The figure below shows the process described above in a highly simplified fashion.



[252] Der Experimentator: Neurowissenschaften, ISBN: 978-3-8274-2368-9, Seiten 7-32; DOI 10.1007/978-3-8274-2369-6_1; http://www.springer.com/cda/content/document/cda_downloaddocument/9783827423689-c2.pdf?SGWID=0-0-45-999954-p174010460

Appendix D: Definitions

Point 1 of the Annex of Regulation (EC) No 726/2004:

"Medicinal products developed by means of one of the following biotechnological processes:
— 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." [26]

21 CFR 601.2(a) "specified biological products":

"…An application for any of the following specified categories of biological products subject to licensure shall be handled as set forth in paragraph (c) of this section:
(1) Therapeutic DNA plasmid products;
(2) Therapeutic synthetic peptide products of 40 or fewer amino acids;
(3) Monoclonal antibody products for in vivo use; and
(4) Therapeutic recombinant DNA-derived products." [27]

Article 1 of Directive 2001/83/EC

"2. Medicinal product:
(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis." [28]

Part I of Appendix I of Directive 2001/83/EC

"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…." [28]

Section 3.1 of the EMA similar products guidance document:

"A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established.

In principle, the concept of biosimilarity is applicable to any biological medicinal product. However, in practice, the success of developing a biosimilar will depend on the ability to produce a medicinal product which is similar to the reference medicinal product, and to convincingly demonstrate the similar nature of the concerned products…" [30]

Section 201(g) of the FD&C Act:

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[26] Regulation (EC) No 726/2004 Article 3(1) and Point 1 of the Annex; OJ L 136, 30.4.2004, p. 1, Consolidated version 05.06.2013; http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

[27] 21 CFR §601.2(a); April 2014; http://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol7/pdf/CFR-2014-title21-vol7-part601.pdf

[28] Directive 2001/83/EC Title I, Definitions of Article 1; OJ L 311, 28.11.2001, p. 67, Consolidated version 16/11/2012; http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[30] Guideline on similar biological medicinal products; CHMP/437/04 Rev 1, 23 October 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

"(g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)." [31]

Section 351(i)(1) of the PHS Act:

"(1) The term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." [32]

Section 351(i)(2) of the PHS Act:

"(2) The term "biosimilar" or "biosimilarity", in reference to a biological product that is the subject of an application under subsection (k), means-
(A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and
(B) there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." [32]

[31] 21 USC §321(g); April 2015; http://uscode.house.gov/view.xhtml?req=%28title:21%20section:321%20edition:prelim%29%20OR%20%28granuleid:USC-prelim-title21-section321%29&f=treesort&edition=prelim&num=0&jumpTo=true

[32] 42 USC §262 (i)(1), 42 USC §262 (i)(2)(A),(B); April 2015; http://uscode.house.gov/view.xhtml?req=%28title:42%20section:262%20edition:prelim%29%20OR%20%28granuleid:USC-prelim-title42-section262%29&f=treesort&edition=prelim&num=0&jumpTo=true

Appendix E: The most significant changes with Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

1. Legal form is now that of a Regulation
2. EU-Portal and electronic database (Article 80, 81) that enables a streamlined application procedure and which is managed by the EMA
3. Compilation of only one application dossier (IMPD) containing the information of Annex I of the REGULATION
4. Member states are requested to meet timelines of Articles 6 and 7 when involving national Ethics committees (Article 4)
5. Harmonized assessment and decision procedure with specified timelines (Articles 6-8)
6. Amplification of the tacit approval method in Articles 6-8
7. Ease of reporting procedures by using the electronic EU-database (Article 40)
8. Depending on the clinical protocol requirements certain adverse events may not require to be reported (Article 41)
9. Cooperation between the EU-Member sates (Article 44) regarding the assessment of information required in Article 42 and 43
10. Articles 25 and 79 specifying conditions of non-EU clinical trials
11. Improved transparency belonging clinical trial information and publication of clinical trial results also of negative outcomes, by using the electronic EU database (Article 81) and several notification requirements (Article 37)
12. The GMP DIRECTIVE 2003/94/EC and the GCP DIRECTIVE 2005/28/EC, in so far they concern clinical trials, will be replaced by other regulations (Article 63 relates to GMP, Article 78 relates to GCP)

Appendix F: Significant differences between the clinical trials Regulation (EC) No 536/2014 and 21 CFR Part 312 IND

Regulation (EC) No 536/2014	21 CFR Part 312 IND
Focus is on clinical trials at all and their adequate conducting	Focus is on new drugs – within an IND the FDA supports for example the drug development, the planned design of clinical investigations, reviews the adequateness of clinical investigations in the view of the quality of gathered data/marketing approval, etc.,
Whereas Section '12': Regulation uses Risk categories A, B, C for CT as specified in OECD Recommendation on the Governance of Clinical Trials of 10. December 2012	-
Article 2 provides definition of "Clinical study" and "Clinical trial". A Clinical trial is a category of a clinical study	§312.3(b) Definition of "Clinical investigation"
Article 3 defines the objectives of this regulation regarding to clinical trials: goals are to protect the human being participating the clinical trial, generation of solid and robust data	§312.1(a) Scope of an IND is to allow shipping of non-approved drugs by law thru the US for the purpose of clinical investigations (Exemption from pre-market approval requirements) §312.22(a) IND objectives: Overall: ensuring safety and rights of the subjects; Phase I: safety assessment; Phase II and III: help ensuring qualitative adequate scientific evaluation of the investigated drug and assessment of the scientific quality of the clinical data in order to review the statutory appropriateness of the gathered scientific data for marketing approval
Article 5 and Article 80 submission of an application trough the EU-Portal developed, maintained and managed by the EMA Validation of the CT application within 10 days after submission from NCA of the EU-member state concerned	§312.20(a) IND submission to the FDA

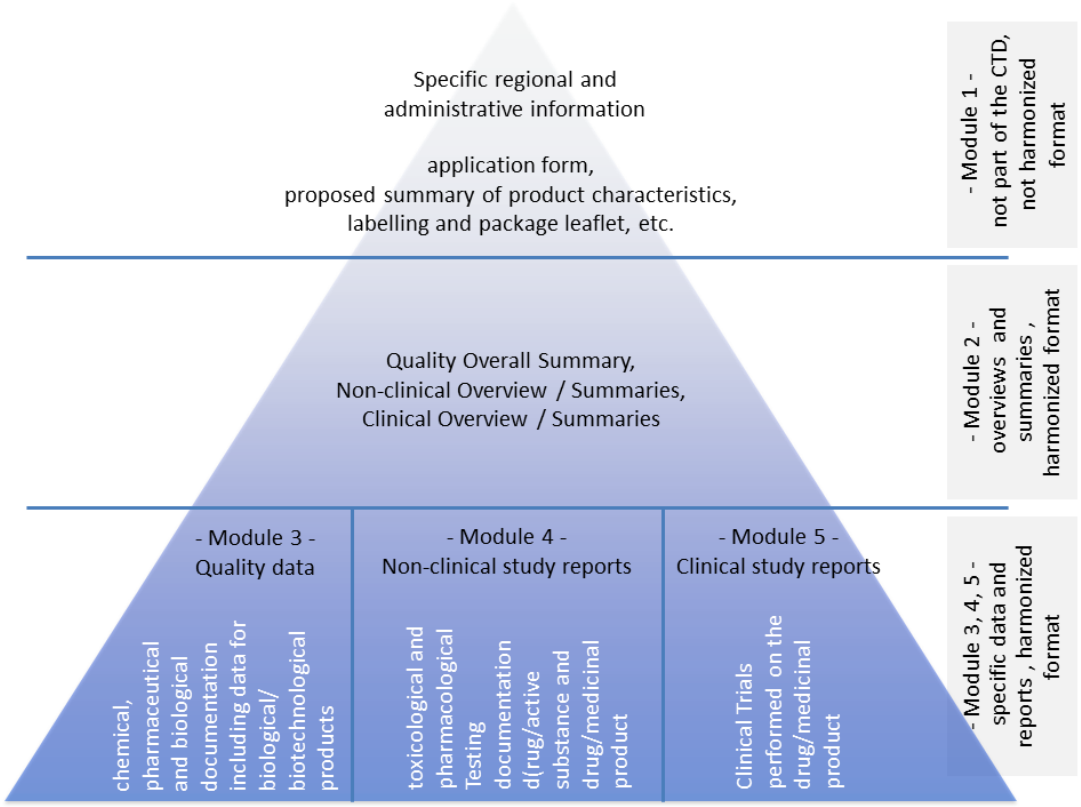
Regulation (EC) No 536/2014	21 CFR Part 312 IND
Article 6 timelines Assessment report –Part I: within 45 days from the validation date the final Part I including its outcome shall be submitted through the EU-Portal to the sponsor and EU-MS Period may be extended to 95 days in total for CT on ATMPs or drug products as defined in point 1 of the Annex to REGULATION (EC) No 726/2004 (BIOLOGICALS discussed within this dissertation)	N/A
Article 7 timelines Assessment report –Part II: within 45 days from the validation date the final Part II including its outcome shall be submitted through the EU-Portal to the sponsor	N/A
Article 8 Decision on the CT application shall be a single decision published to the sponsor via EU-Portal within 5 days from last assessment day (Article 7). The decision of the Part I assessment is the more crucial decision of both Parts.	§312.40(b)(1): IND goes into effect 30 days after FDA has received the IND submission or (b)2 on earlier written notification. FDA will confirm the IND receiving date with the sponsor
Article 8 After two years from CT approval date the CT approval expires if no study subjects have been recruited unless the sponsor applies for extension	§312.45 After ≥two years from CT approval date the CT approval turns into an inactive status if no study subjects have been recruited. Prior to change the IND status FDA will notify the sponsor §312.44 After ≥five years of inactive status of an IND the IND will be terminated by the FDA
Article 12 withdrawal possible at any time until the reporting date. Reason for CT withdrawal shall be published via EU-Portal	§312.38(a) an effective IND could be withdrawn at any time §312.38(b): FDA shall be informed after the IND is withdrawn §312.38(c):If an Safety issue is reason for the withdrawal of an IND the FDA shall be informed promptly and the reason for the withdrawal shall be provided
Articles 18-23 assessment and decision on substantial modifications to the CT	§312.30(b)(1) changes in a protocol that significantly affects the subjects safety
Article 36 Notifications: start of CT within 15 days from start of the CT; First visit of the first subject within 15 days from the first visit; End of subject recruitment within 15 days after end	N/A

Regulation (EC) No 536/2014	21 CFR Part 312 IND
Article 38 temporary halt or early termination of the CT by the sponsor due to subject safety (affecting risk-benefit) without delay and within 15 days starting from the hold date/termination date	§312.56 (d) if the sponsor realizes an unreasonable and significant risk of the investigational drug to subjects the sponsor shall notify FDA and shall stop the relevant investigation asap but no later than 5 working days after the decision to stop the investigation was made
Article 37 sponsor shall notify about the end of a CT within 15 days from the end of the CT; Within one year after the CT has ended a summary report and a report understandable to non-qualified persons shall be published through the EU-CT-database and with regard to MAA the clinical study report shall be published through the EU-CT-database within 30 days after MAA has been received	N/A
Article 41 Investigator shall report serious adverse events to the sponsor without delay within 24 hours of becoming aware of the event	312.64(b) Investigator must report serious adverse events to the sponsor immediately after of becoming aware of the event
Article 42 reporting line for suspected unexpected serious adverse reactions: fatal or life-threatening SUSARs ASAP but within 7 days after notice Non-fatal or non- life-threatening SUSARs within 15 days after notice Non-fatal or non- life-threatening SUSARs which later turn into fatal or life-threatening SUSARs: ASAP but within 7 days after notice	§312.32 reporting time line of max. 15 days for §312.32 c (1)(i), c (1)(ii), c (1)(iii), c (1)(iv) after the sponsor determines that the event is one out of the listed cases: 1. Non-fatal or non- life-threatening SUSARs after notice (same as in the EU), 2. Findings from other studies, 3. Findings from animal or in vitro testing, 4. Increased rate of occurrence of serious suspected adverse reactions §312.32(v): provide additional data to FDA upon request within 15 days after requested (§312.32(2) reporting time line for fatal or life-threatening SUSARs asap but within 7 days after receipt of event information→same as in the EU)
Article 52 serious deviations from Clinical protocol or regulation shall be reported without delay but within 7 days of sponsor becomes aware of it	§312.56(b) deviations by the investigator from the agreed clinical documents or 21 CFR 312 shall be reported to the FDA by the sponsor if the investigators participation on the trial is ended because of this deviation

Regulation (EC) No 536/2014	21 CFR Part 312 IND
Article 53 Unexpected events which affect the subject safety shall be reported without delay but within 15 days sponsor becomes aware of it	Refer to §312.32 reporting time line of max. 15 days for §312.32 c (1)(i), c (1)(ii), c (1)(iii), c (1)(iv)
Article 54 Urgent safety measures in case of serious events related to subject safety: notification through the EU portal without delay but within 7 days from the date the measures were implemented	N/A
Article 57 clinical trial master file for sponsor and investigator	§312.62 (b) case histories and other records §312.57
Article 58 Archiving of the Clinical trial MF 25 years after the clinical trial	§312.57 records related to the investigational drug(a) and financial interest (b) shall be kept, retention time for these records and reports is for 2 years after the date of marketing approval §312.57 (d) sponsor shall keep reserve samples of test articles and reference standards as specified in §320.38, §320.63 with a retention time of 5 years after the date of marketing approval §312.62 (c) case history record retention time for 2 years after the date of marketing approval
Article 61 qualified person acc Article 49(2) Dir 2001/83/EC	N/A
Article 66 Labelling requirements (outer and immediate): Goal is to ensure subject safety and solid generated data	§312.6 Labelling on immediate packaging, Goal is to show it is an IND approved investigational device. It must not claim misleading or not proven information
Article 76 Damage compensation	N/A
Article 77 clinical trial – corrective measures: before they will take place the applicant gets 7 days' time to give its opinion	§312.42 (d) sponsor will be informed by the FDA by phone or other fast communication about the imposition of the clinical hold and receives within 30 days a written statement to the clinical hold issue §312.42 (c) where possible, before issuing a clinical hold the FDA allows discussion of the deficiency in order to solve it
N/A	§312.41 (a), (b) The FDA provides advice upon sponsors request on an IND. The FDA may be request additional data or comments on deficiencies at any time during the IND
N/A	§312.47 meetings with the FDA

Regulation (EC) No 536/2014	21 CFR Part 312 IND
N/A	Subpart E provisions (drugs to treat life-threatening and severely-debilitating illness) e.g. §312.82 early consultation (e.g. Pre-IND) possibility in order to reach agreement on the planned studies and testings as well as to clarify pediatric aspects all in the light of the aimed marketing approval or §312.87 Active monitoring of clinical trials

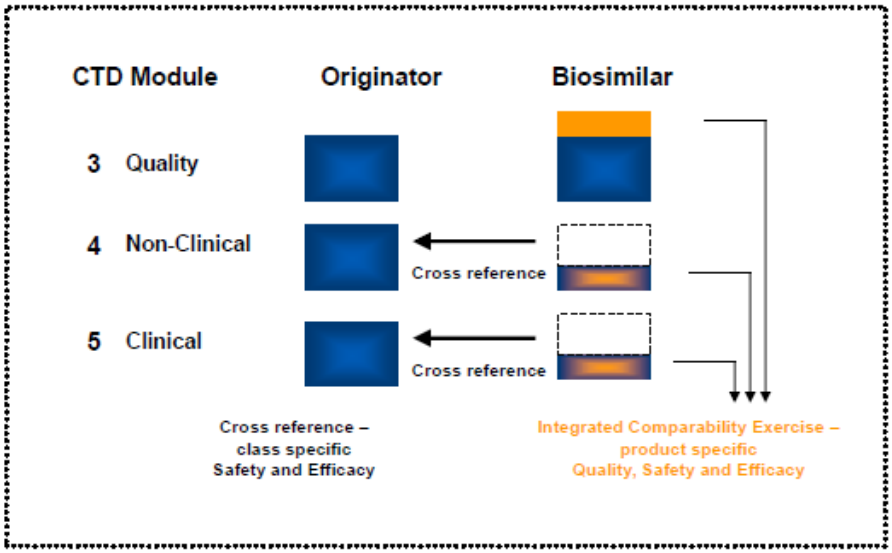
Appendix G: The modules of the CTD format, guideline documents and contents



Appendix H: EU-Dossier requirements for biosimilar products and biological originator products

As illustrated are full quality data plus comparability data required for a biosimilar products application while the volume of non-clinical and clinical data is less, [4] Graphic © by European Medicines Agency

Dossier requirements for Biosimilars



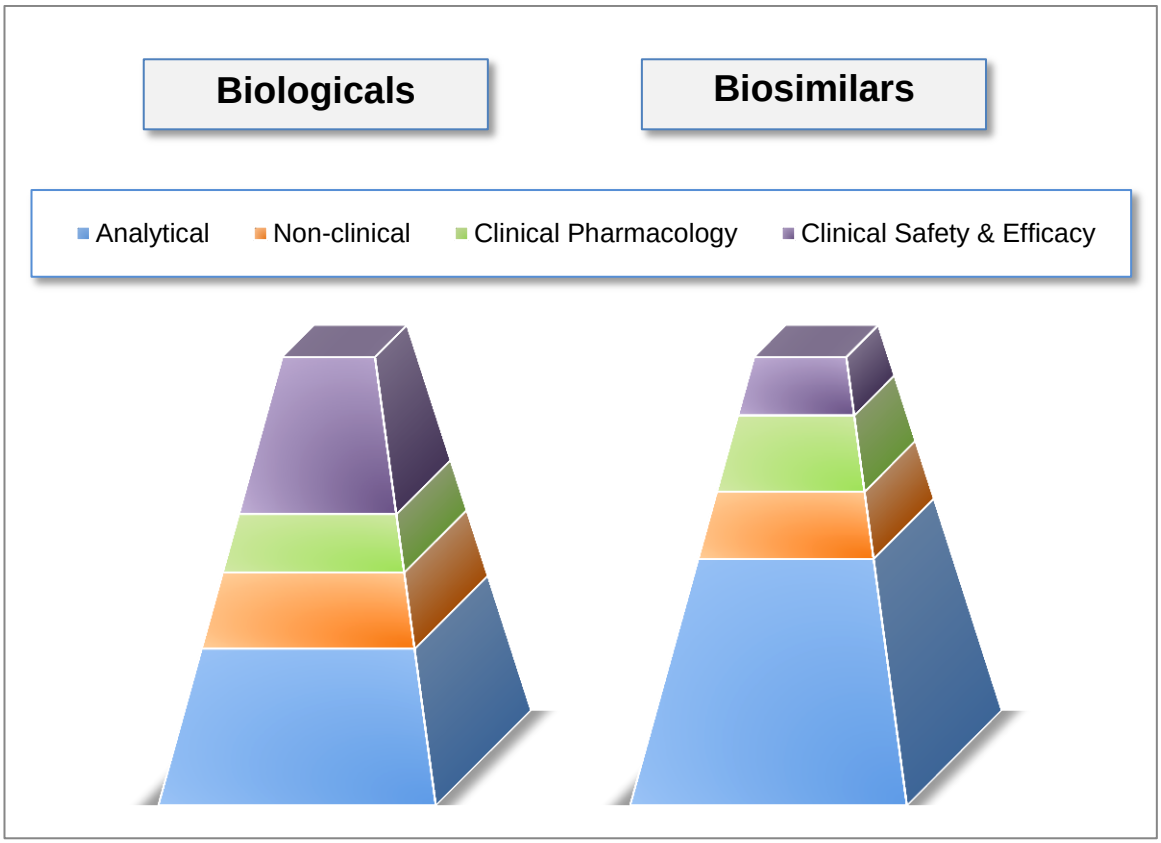
A biosimilar product application dossier shall provide a full quality dossier and data demonstrating comparability with the reference medicinal product by using appropriate physico-chemical and in vitro biological tests, non-clinical studies and clinical studies. [57]

[4] ICH GCG ASEAN Training Workshop on ICH Q5C, 30-31 May 2011, Kuala Lumpur; Alberto Ganan Jimenez & Brigitte Brake; http://www.ich.org/fileadmin/Public_Web_Site/Training/ASEAN_Q5C_workshop_May_2011/SESSION_IVa_Biosimilars.pdf

[57] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev1, 18 December 2014; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf

Appendix I: Approximate dossier shares of the specific parts in BLA application dossiers and abbreviated BLA application dossiers

Please note, diagram and values are not to scale. The diagram only intends to visualize the differences on an approximately basis and to highlight the major differences between the data content and volume of a biosimilar products application versus those of biological products. As illustrated is the volume of analytical data that have to be generated for biosimilar products much higher, while the clinical safety and efficacy data are less.



Appendix J: Significant safety-relevant regulatory standards as established by EU legislation (Directive)

Directive 2001/83/EC, consolidated version 16.11.2012

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
Article 6: authorization requirement for medicinal products prior to marketing	Article 11: add standard sentences in SmPC labeling in order to promote the reporting of suspected adverse reactions (SAR) by healthcare professionals	
Article 8(1): drug application to the competent authorities Article 8(2): applicant being established in the EEA Article 8(3): specifies the documents that must be submitted within a market authorization application e.g., Article 8 (3)(c) requires international non-proprietary name (INN) recommended by the WHO, if available Article 8(3)(ca): environmental assessment Article 8 (3)(iaa) and (m): risk management plan and risk management system	Article 21: European Public Assessment Report (EPAR) requirement Article 21a: defines further post-authorization measures that the applicant shall take (e.g., post-authorization efficacy studies (PAES))	Article 41: the manufacturer must use the service of a qualified person

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
Article 10(2)(a): defines the 'reference product' "'reference medicinal product' shall mean a medicinal product authorised under Article 6, in accordance with the provisions of Article 8;"	Article 22 and 22a: allows national competent authorities to require further post-authorization measures (PAMs)	Article 46: defines duties of the holder of a manufacturing authorization and specifically points out compliance with good manufacturing practice and good distribution guidelines. The holder of a manufacturing authorization must conduct self-inspections, must allow competent authority inspections at any time, must use the tool of a formalized risk assessment and must have an implemented quality system. If there is a suspicion that one of its medicinal products got falsified then the manufacturing authorization holder must report this to the competent authorities and to the MAH. The manufacturing authorization holder must also verify that its suppliers, importers and distributors of active substances are registered with the competent authority and must verify originality of the active substances and excipients and must qualitatively check them

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
Article 11: defines minimum requirements for the summary of the product characteristics (SmPc) and details the requirements laid down in Article 23 of the Regulation (EC) No 726/2004 for medicinal products under additional monitoring, listed drugs must be identified by a black symbol.	Article 23 and 23b(1): requires that the marketing authorization holder keeps its drug related processes to the latest state of the art, technically and scientifically, and also requires of the MAH the reporting to and approval of any changes that may influence the approved drug, by the national competent authority. Article 23b(1): further requires from the European Commission to provide an instrument for examining variations (variation-system) Article 23(a) at minimum 2 month before a product is taken temporarly or permanently from market the MAH shall notifiy the competent authority.	Article 51: requires in paragraph 1 that the qualified person shall secure that: a) "in the case of medicinal products manufactured within the Member States concerned, that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorization; b) In the case of medicinal products coming from third countries, irrespective of whether the product has been manufactured in the Community, that each production batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorization". (pre- and post-authorization)
Article 19: defines the actions and instruments of the authorities in order to allow reliable and scientific based decisions regarding a drug application	Article 24: limits the validity of a marketing authorization to five years and requires undergoing a once-only renewal afterwards	Article 52a: registration of importers, manufacturers and distributors of active substances that have its business in the EU

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
Article 20: requires that competent authorities shall verify the compliance with the legal requirements of third country manufacturers and importers and shall ensure that third parties used as sub-manufacturers are compliant (e.g. by performing inspections)	Article 31(4): allows the competent authorities to suspend the marketing authorization (post-authorization) of medicinal drugs approved under the Centralized Procedure	Article 55: defines the information to be shown on primary packaging/blister packs.
Article 40: requires a manufacturing authorization for drug production, -filling, -packaging and -presentation and an import authorization for third country imports	Article 54: defines the required safety features of the outer packaging Article 54(a) outer packaging must show the international non-proprietary name (INN), if available or the common name of the active substance (for up to three active substances contained in the drug) Article 54a(4) requires that the national competent authorities shall list non-prescription medicinal products with having a risk of getting falsified and provide this list to the European Commission	Article 56: requires clarity, readability and inextinguishably for the information displayed on the packaging and the Article 56a requires the drug name on the packaging in braille format
Article 42: requires that the manufacturer is inspected by the authorities prior to receive the manufacturing authorization	Article 64: gives the competent authority the right to suspend the marketing authorization until the labeling is corrected and in accordance to the legal requirements	Article 58: requires an package leaflet
Article 70: classification of medicinal products into non-medical prescriptive and medical prescriptive	Article 74: changes from the authorities regarding to the classification of medicinal products	Article 59: defines contents of the package leaflet and requires a proof of readability
	Article 101 and 102: requires the member states to run a pharmacovigilance system, to self-audit these and details the content of a pharmacovigilance system	Article 63: requires that relevant information (please refer to Articles 54, 59, 62 of the DIRECTIVE) are available in languages of the EU countries where the drug is marketed (pre- and post-authorization)

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
	Article 107: requires the MAH to gather information related to suspected adverse reactions, to scientifically analyze these data and to report them via internet-portal (EudraVigilance), within clinical trials such information shall be handled according Directive 2001/20/EC; reporting requirement of 15 days for serious suspected adverse reactions after receiving the information reporting requirementof 90 days for non-serious suspected adverse reactions after receiving the information, all information regarding to adverse have to be provided online via EudraVigilance Database (Article 24 of Regulation (EC) No. 726/2004)	Article 76: requires a marketing authorization for medicinal products´ wholesale distribution and storage and a wholesale authorization (which is included in the manufacturing authorization)
	Article 107a: requires the EU member states to collect, analyze and report adverse data as described in Article 107	Article 77: requires authority inspections of wholesalers
	Article 107b: requires the MAH to submit periodic safety update reports (PSUR) to the EMA	Article 80: defines items that have to be fulfilled from wholesale authorization holders (distributors) e.g., full track and trace system, quality system, risk management, keeping distribution records
	Article 107h: requires the national competent authorities and the EMA to follow up on manufacturer actions minimizing the risk, to analyze EudraVigilance-data and to react accordingly to the outcome)	Article 104: requires the MAH to run a pharmacovigilance system and a risk management system and to analyze obtained data, MAH pharmacovigilance self-inspections

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
	Article 107i: authorizes the competent authorities and EMA to initiate a procedure to revoke, suspend or refuse a marketing authorization or renewal, or to stop distribution	Article 111: allows authorities to conduct unannounced inspections at any time
	Article 107n-q: details the supervision of post-authorization safety studies	
	Article 116: suspension, revocation and withdrawal of marketing authorizations thru the competent authorities because , of safety and other reasons	
	Article 117a: requires a national system to avoid distribution of harmful and falsified medicinal products	

Appendix K: Significant safety relevant regulatory standards as established by EU legislation (Regulation)

Regulation (EC) 726/2004, consolidated version 05.06.2013

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
Article 2: MA holder must be established in the Union market community.	Articles 10a: Post-marketing obligations to the MAH: PASS, PAES and further measures supplementing the obligations	Article 18: Monitoring of the manufacturing and the Pharmacovigilance system on national level, Manufacturing authorization, link to Article 40(3) 2001/81/EC
Article 3: Authorization requirement for medicinal products prior to marketing Article 3 (3): The reference product of a generic must be a medicinal product authorized within the EU.	Article 3 (3) only refers to generics and Article 3(3)(c) only talks about the name and linguistic version of the INN for generics,	
	Article 13 (1): approved medicinal products to be entered into the Community register under issuing a specific registration number, Article 13(2) marketing authorization is published in the Official Journal of the European Union including the INN of the active substance Article 13 (3) MAH to notify the Agency if the product marketing is interrupted, temporarily or permanently. The notification shall be made at minimum 2 months before the interruption happens.	Article 19: Regarding to national level responsibilities links are given to Title IV ("Manufacture and Importation") and XI ("Supervision and Sanctions") of 2001/83/EC Also on national level is the monitoring of manufacturer as well as monitoring of Pharmacovigilance and relevant Inspections on national level (link to Titles IX ("Pharmacovigilance") and XI of 2001/83/EC)
Article 4: Community to grant and supervise the marketing authorization through CHMP (established with Article 5)	Article 14, 14a: MA renewal after 5 years, implementation of defined conditions into the MAH Risk management system	Article 27: Monitoring of literature through the EMA and maintenance of Eudravigilance

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
Article 6: Documents required in an application – link to Directive 2001/83/EC Articles 8(3), 10, 10a, 10b or 11. With regard to genetically modified organisms (GMO) a link to the requirements of Directive 2001/18/EC or Directive 90/220/EEC is given	Article 16: Approval of changes/variations, actuality of the Pharmacovigilance-system master file, duty to supply defined information	
Article 7: Medicinal product in application, its starting material and other can be tested in an official medicines control laboratory in order to the opinion preparation process through the committee for human medicinal products	Article 20: Procedure for the suspension of the MAA by member states	
Article 8: (unannounced) inspections as part of the application examination process by the committee CHMP	Article 21: Pharmacovigilance Link to article 104 of 2001/83/EG	
Articles 12: Refusal of marketing authorization	Article 22: Safety announcements and link to article 106a(1) of the 2001/83/EC	
	Article 23: Black symbol list –extended monitoring	
	Article 24: Eudravigilance database	
	Article 28: Recording and reporting of SARs, link to article 107, 107(a), (b), (c) of 2001/83/EC	
	Article 28a and b: Measures for approved medicinal products taken by EMA and on national level, non-interventional PASS with link to Articles 107m, 107n-107p and 107q of 2001/83/EC	

Appendix L: Significant biological specific safety relevant regulatory requirements as established by US legislation

21 CFR Part 600-680, 42 USC §262 of the PHS and 21 USC §§ 301 et seq.of the FD&C Act

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
21 CFR 601.2 Applications for biologics licenses; procedures for filing: Requirement of BLA submission prior to obtain approval under section 351 of the Public Health Service Act (Please also refer to 42 USC 262(a)) BLA approval is based on meeting applicable requirements to the establishment(s) and the biological product- these requirements shall ensure the continued safety, purity, and potency of biological products. Submitted data shall be originated from: -non-clinical laboratory studies, -clinical studies that demonstrate that the applied product "…meets prescribed requirements of safety, purity, and potency; with respect to each nonclinical laboratory study…" -and, for licensure applications for biosimilar the 42 USC 262(k)(2)(i) requires data demonstrating biosimilarity and, if so, interchangeability to one FDA approved reference product (42USC 262(k)(5)(A)). In view of the product interchangeability the 42 USC 262(k)(4)defines safety standards that must be fulfilled by the biosimilar product In 42 USC 262(a)(2)(B) the submission of assessments to pediatric studies as defined in	21 CFR 600.14 Reporting of biological product deviations by licensed manufacturers - report quality or safety related deviations of products realized after products release into the market as soon as possible but no later than 45 calendar days after the deviation has occurred using the FDA Form 3486 – performance of investigations of deviations in accordance with 21 CFR Part 211 (cGMP)	21 CFR 600.10 Personnel: specifies qualifications, restrictions and hygienic requirements to personnel in specific functions, requirements for Pathogenic viruses or spore-forming organisms, etc., Risk Evaluation and Mitigation strategies as defined in sections 505(o), 505(p), and 505-1 of the FD&C Act (21 USC 355(o), (p); 355-1) 21 CFR 314.50(a)(5) US agent

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
section 505B of the FD&C Act (21 USC 355c) [253] is required unless waived: -The 21 USC 355c(m)(1) defines that biosimilars found to be non-interchangeable (42 USC 262(k)(4)) to a reference product as new active ingredient and therefore a need to submit pediatric assessment data, unless waived -The 21 USC 355c(m)(2) considers biosimilars interchangeable to a reference product not as new active ingredient and therefore the conduct of pediatric clinical trials and submission of pediatric assessment data is not necessaryGeneral Data requirements and submission content are given; need for environmental assessment under § 25.40 or claim for exclusion under § 25.30 or § 25.31; Monoclonal antibody products and recombinant DNA derived products are categorized as specified biologics and following sections are not applicable to these products: 21 CFR 600.10(b) and (c); 600.11, 600.12, 600.13, 610.53, 610.62		
21 CFR 601.4 Issuance and denial of license: Denial of a biologics license application when the establishment or product does not meet the requirements set out in 21 CFR	21 CFR 600.80 Postmarketing reporting of adverse experiences Review of adverse experiences: prompt review required Individual case safety reports (ICSR) and information to be provided Reporting requirements: Postmarketing 15 day Alert Reports: report serious and unexpected asap	21 CFR 600.11 Physical establishment, equipment, animals, and care: specifies hygienic standards for manufacturing and warehouse areas, equipment or requirements for spore-forming organisms, animals and disease reporting, etc., 21 CFR 310.305 Records and reports concerning adverse drug experiences of marketed prescription

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
	but no later than 15 calendar days after the initial receipt of the information; reporting of periodic safety reports Postmarketing 15 day Alert Reports – follow up: submission of follow-up reports within 15 calendar days or on FDA requested Periodic adverse experience reports: every 3 month for the first 3 years after the BLA got approved, from fourth year on an annual basis Recordkeeping: 10 years for adverse experiences Revocation of biologics license: if BLA owner fails establishing and keeping records or if he fails to make postmarketing reports required by section §600.80 the FDA can revoke its BLA Scientific literature. A 15-day Alert report based on information in the scientific literature including a copy of the published article 21 CFR 601.28 Approved BLA Annual Reports (21CFR 314.80 and 21 CFR 314.98 Postmarketing reporting of adverse drug experiences; 21 CFR 314.81 Other postmarketing reports: Annual report (applicable to common drug products) 42 USC 262(a)(2)(D) and 42 USC 262(k)(5)(C) (21 USC 505(o)(3); (p) and 505-1) FDA may require Postmarketing studies and Risk evaluation and mitigation strategy (REMS)	drugs for human use without approved new drug applications
21 CFR 601.20 Biologics licenses; issuance and conditions Approval is given only when the product complies	21 CFR 600.81 Distribution reports CDER shall be informed about the distributed quantities of products licensed under BLA every 6	21 CFR 600.20 and 21 CFR 600.21 Establishment inspections of licensed manufacturers and manufacturers applying for BLA performed by the

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
with all relevant requirements, when the product is available for examination and product production inspection, when the manufacturing process assures the consistency of products safety, purity, and potency, after the successful FDA inspection of all manufacturing facilities mentioned in the license	month. Temporary waivers may be possible.	FDA (please also refer to 42 USC 262(c)). Once every 2 years an inspection of BLA licensed establishments will be performed – with or without prior notice
Furthermore: Establishment (facility) registration and drug listing: Establishments must be registered within 5 days of beginning operations. (21 CFR 207.21(a) and 207.40 and FD&C Act 21 USC 510(c), (d), & (i)). In addition, establishments must renew registration annually between October 1st and December 31st of each year. (21 USC 510(b) & (i)).	21 CFR 601.2 Applications for biologics licenses; procedures for filing - Link to PHS Act (42 U.S.C. 201 et seq.) that authorizes the FDA to promptly suspend biologic licenses if needed to protect public health (license suspension)	21 CFR 601.2 Applications for biologics licenses; procedures for filing Link to GMP requirements under 21 CFR 210, -211, -600, -606 is given
21 CFR 312 IND approval requirement prior to conduct a clinical trial 21 CFR 312.32 Investigational New Drug Safety Reports 42 U.S.C. § 282(j), and section 402(j) Act register the clinical trial in ClinicalTrials.gov. database	21 CFR 601.4 Issuance and denial of license validity of a biologics license: until their suspension or revocation	21 CFR 601.15 Foreign establishments and products: samples for each importation: random samples of imported products being forwarded to CDER/CBER must consist of two final containers of each product lot including relevant shipping and identification documents for imports greater than 20 containers
	21 CFR 601.5 Revocation of license: e.g., -when the FDA cannot perform an inspection in accordance to § 600.21 -a change was not reported as required by § 601.12 -any other circumstances where the approved drug or establishment does not meet the requirements of	42 USC 262(d) FDA may order a recall of hazardous products

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
	21 CFR or the applicable standards set out in the biologics license -etc.,	
	21 CFR 601.6 Suspension of license: e.g., in situations representing a danger to public health	
	21 CFR 601.12 Changes to an approved application The manufacturer must inform the FDA about each change in the biological product, manufacturing process, quality controls, equipment, facilities, responsible personnel, or labeling set out in the approved BLA. Prior distribution of a product involved in any change the license holder must assess the change with respect to its effects. Validations and/or further studies must demonstrate that the change has no influence to the products safety or effectiveness. Three categories of changes (major, moderate, minor) with different approval FDA conditions (general FDA approval prior distribution for major supplement submissions, 30days prior distribution approval by FDA of supplement submissions for moderate changes and no prior FDA approval for minor changes, only notification in annual report) The FDA may require a license holder to always submit a supplement for any intended change that must be FDA approved prior product distribution in case of repeated failure to comply with the change reporting requirements	

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
	(Like EU-Variation system)	
	21 CFR 601.70 Annual progress reports of postmarketing studies: Annual progress reports of postmarketing studies including Form FDA–2252	21 USC 331 Prohibited acts 21 USC 331 (i)(3) prohibition of counterfeit drugs 21 USC 355e Pharmaceutical security 21 USC 355e(a); 355(c)(1) 21 USC 360bbb-7 Notification requirement by awareness of counterfeit drugs
	21 CFR 610.1 Tests prior to release required for each lot: Each lot must be tested for its conformity with standards applicable for this product after completion of its manufacturing process Final release testing requirement	21 USC 502(e)(3) and 21 CFR 299.4 Established (official) drug name provided by the FDA
	21 CFR 610.2 Requests for samples and protocols; official release: The FDA may require lot samples including its release testing protocols for official release. (not typical for specified biologics) FDA official release requirement (FDA batch prerelease)	
	21 CFR 610.9 Equivalent methods and processes. Requirements prior permission to modify specific test methods or manufacturing processes or conditions (please also refer to § 601.12)	
	21 CFR 610.10 Potency – requirements for potency testing	
	21 CFR 610.12 Sterility –	

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
	Requirement to perform sterility testing of each lot of each final container material. If the CDER responsible person determines the data submitted with the BLA of BLA supplement are adequate enough to preclude or show un-necessity of sterility testing it can be waived.	
	21 CFR 610.13 Purity – product is required to be free of extraneous material. Beside purity testing further testing shall be performed: residual moisture testing on each lot of dried product testing for pyrogenic substances on each lot of final containers (for injection products) by intravenous injection into rabbits with a testing dose of at least 3 milliliters per kilogram of body weight 21 CFR 610.14 Identity – identity testing to be performed on the contents of a final container of each filling of each lot after all labeling operations have been finished	
	21 CFR 610.18 Cultures – Requirements for storage and maintenance, Identification and verification, Cell lines used for manufacturing and testing.	
	21 CFR 201.57(c)(1): Boxed Warning to ensure safe use because of the drug product	
	21 CFR 601.42 Approval with restrictions to assure safe use (regarding distribution or use)	

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
	Labeling requirements 21 CFR 610.60 Container label – content requirements 21 CFR 610.61 Package label (please also refer to 42 USC 262(a)(1)(B)) 21 CFR 610.62 Proper name; package label; legible type 21 CFR 610.63 Divided manufacturing responsibility to be shown 21 CFR 610.64 Name and address of distributor. 21 CFR 610.65 Products for export 21 CFR 610.67 Bar code label requirements 21 CFR 601.25(d)(5) clear labeling, no false or misleading information Medication Guide in compliance with part 21 CFR 208 Furthermore: Labeling requirements: information required in and format as specified by 21 CFR §§ 201.56, -201.57, and -201.80 as well as in addition to the provisions of 21 §§ 601.2(a) and 601.12(f); requirements in 21 USC sections 502 and 503 of the Federal Food, Drug, and Cosmetic Act, 21 CFR 210 & 21 CFR 211 cGMP 42 USC §262(b) no falsely labeling or marking	
	21 USC 356c Discontinuance or interruption in the production of life-saving drugs (requires to notify the FDA 6 month prior potential interruption); Cited from Federal Register / Vol. 78, No. 213 / Monday, November 4, 2013 / Proposed Rules:	

Pre-authorization	Post-authorization	Overall (pre-and post-authorization)
	"…to notify FDA electronically of a permanent discontinuance or an interruption in manufacturing of the product that is likely to lead to a meaningful disruption in supply (for drugs and biological products other than blood or blood components) or a significant disruption in supply (for blood or blood components) of the product in the United States 21 USC § 356c (i)(3) Inclusion of biological products (21 CFR 310.306, 314.81(b)(3)(iii), and 21 CFR 600.82 (a)(1))	
	21 U.S.C. 355(r) Postmarket drug safety information for patients and providers (improves transparency by publishing/posting the summaries of postmarket safety evaluations of adverse experience reports)	

Appendix M: Overview of significant similarities and differences between regulatory and scientific requirements in the EEA and USA

Item	EEA	USA
Overall safety-relevant regulatory requirements		
Definition of biological product	Product, which contains a biological substance that is produced or extracted from a biological source. To characterize the product and to determine its quality physico-chemical and biological testing and a well-controlled production process is needed	Product, which is derived from living materials, such as as human, animal or microorganisms. Such products are complex in nature and usually not fully characterizable
Comment	The overall definition of biological medicinal products is very similar. Both regions refer to the biological source.	
Definition of biosimilar / biosimilarity	Biological product that contains a version of the active substance of an authorized biological innovator product (reference product). Biosimilarity to the reference product must be established by comparability testing and must be demonstrated for of quality characteristics, biological activity, safety and efficacy	Biological product that is highly similar to the biological reference product by means of that no clinically meaningful differences exist between these products in terms of product safety, purity, and potency
Comment	Both, the EEA and the USA refer in terms of the similarity to a reference product and to require a similar safety. The US legislation additionally clarifies the term “highly similar” by requiring no clinically meaningful differences between the both products	
Definition of monoclonal antibodies and recombinant protein products	Biological medicinal product	Specified biological products [27]. Defined exclusions (21 CFR §§ 600.10(b) and (c), 600.11, 600.12, 600.13, 610.53, and 610.62) apply

Item	EEA	USA
Regulatory approval pathway for biological and biosimilar products considered	Biological products: Centralized Procedure with full application dossier according to Article 8 of Directive 2001/83/EC [26] [28] Considered biosimilar products (mAbs, recombinant protein products): Centralized Procedure with full application dossier according to Article 8 of Directive 2001/83/EC For some biosimilar products an abbreviated application dossier applies but the EMA determines the need of additional data on a case-by-case basis for applications based on to Article 10(4) of Directive 2001/83/EC	Biologics License Application with full licensure dossier as established in 21 CFR § 601.2(a) (biological products) Abbreviated Biologics License Application as established in 21 CFR § 601.2(k) (biosimilar products). FDA determines the need of additional data on a case-by-case basis.
Comment	Abbreviated approval pathways for biosimilar products exist in both regions. However, in the EEA the same approval pathway and dossier requirements as for biological innovator products are mandatory (Centralized procedure).	
Reference product	Must be an original biological product authorized in the EEA, only one and the same reference product shall be used throughout the comparability program. The use of a non-EU licensed reference product may be possible for certain clinical or in-vivo non-clinical studies when comparative bridging data between all three products are provided and the non-EU licensed reference product was authorized by a regulatory authority using a similar level of approval standards like the EMA	Must be a single original biological product licensed by the FDA, only one and the same approved product should be used as reference product. The use of a non-US licensed reference product may be possible for certain comparative clinical or animal non-clinical studies when bridging data between all three products demonstrate comparability. The non-US licensed reference product was authorized by a regulatory authority using a similar level of approval standards like the FDA
Comment	No significant differences exist. The FDA guidance documents, specifically the Q&A guidance document, discussing the topic of using a third-party comparator product and providing more detailed information than the relevant EMA guidance documents.	

Item	EEA	USA
Interchangeability / automatic substitution	The determination of the interchangeability of a biosimilar product with a biological innovator product is not part of dossier review and not an EMA decision. The responsibility to determine a product as interchangeable and decisions about automatic substitution rests with the individual EU member states (decentralized approach).	If requested by the applicant, the interchangeability status as established in 42 USC 262(i)(3) will be reviewed as part of the application. The FDA will determine the interchangeability status. Theoretical, interchangeable products can be automatically substituted for the original product at pharmacy level depending on the grade of US law enforcement at US state law level
Comment	Differences exist. The determination of the interchangeability status and decision regarding an automatic substitution is not an EMA decision with the EEA but is at national level. While it is a FDA decision in the USA where the US law (USC) provides the FDA with the necessary power to determine product interchangeability. Further, once a product is determined interchangeable it can be automatically substituted.	
Exclusivity / protection periods	Usually, 10 years with the Centralized Procedure	12 years
Comment	A difference of 2 years exists.	
Exclusivity period for products found to be interchangeable	Not applicable	Typically, 1 year
Comment	The difference is reasoned by different regulatory approaches regarding the interchangeability status of a product.	
Drug Master File (ASMF, DMF)	Active substance master file is not accepted for biosimilar product authorization application purpose	Drug master file is not accepted for biosimilar product licensure application purpose
	No differences exist.	

Item	EEA	USA
Labeling and naming	Medicinal products shall provide a common name preferably the INN (International Nonproprietary Names) and, if such not exist, the usual common name. For biosimilar products the applicant may either apply the INN used for the reference medicinal product or may request a new INN from the WHO. The WHO INN proposal envisages a biological qualifier (BQ) code that is specifically assigned to all biotechnology-derived substances having or eligible to have INNs. In its basic the biological qualifier is a four letter random alphabetic code that will be added as unique identification code. It is used in conjunction with the INN but will remain independent from the INN. The BQ scheme may be used voluntarily by any regulatory authority and would be recognized worldwide. The INN proposal document does not explain if and how the BQ is eligible to distinguish between interchangeable and non-interchangeable biosimilar products in order to avoid unintentional substitution. Solution for interchangeable biosimilar products is open.	In order to assist applicants in addressing labeling specifics of biosimilar products for submission purpose, the FDA has issued recommendations to industry in a labeling guidance document which provides information to the content of the prescribing information (package insert). However, the labeling of interchangeable biological products is not considered in this guidance. Biological products shall provide a proper name (42 USC §262(a)(1)(B)(i); 21 CFR 600.3(k)). Original biological products shall use a core name that is the adopted name designated by the USAN Council for the relevant biological substance when available. The core name is the component shared among all related biological products as part of the proper name. If the biological product is a biosimilar product, or an interchangeable product, the core name will be the same as the core name identified in the proper name of the relevant innovator product. A product unique suffix that is composed of four lowercase letters will be attached with a hyphen to the core name of each innovator biological product or biosimilar product (e.g., innovator product name replicamab-cznm; biosimilars name replicamab-hixf). For interchangeable products the FDA is still searching for the appropriate suffix format but will use the same approach of that of a core name and a suffix included in the proper name.

Item	EEA	USA
Comment	Differences exist. While the basic concept of a unique four letter code attachment for biological products is the same, in the EEA, this letter code will be provided by the WHO and will amend the INN of biological products. In the USA letter code will be designated by the FDA and attached as suffix to the core name and included in the proper name. While the FDA is searching for a well working suffix solution for interchangeable products, this is not discussed within the EEA and WHO guidance document. There is no EMA guidance document comparable to the FDA´s labeling guidance for biosimilar products available in the EU.	
Prescription information	Directive 2012/52/EU requires brand name instead of INN for biological products. No information to biosimilar and interchangeable products provided.	There is no difference in prescribing of biosimilar and / or interchangeable products and any other medicinal products. Either the proprietary name or the nonproprietary name shall be documented on the prescription
Comment	Differences exist. No information related to biosimilar and interchangeable products is provided in the mentioned EU Directive. In the USA, no differences in the prescribing information of biosimilar and / or interchangeable products and any other medicinal products are made.	
Pediatric assessement	Not required for biosimilar products as the goal of the development program is to establish comparability and thus, the focus in selecting the primary patient population is laid on homogeneity and sensitivity	Required for biosimilar products not determined to be interchangeable as such biosimilar products are considered as new active ingredients (21 U.S:C. 355c). The requirement can be waived or deferred. Not required for biosimilar products determined to be interchangeable as such products are not considered having a new active ingredient.
Comment	Differences exist. The FDA handles the topic tighter and considers pediatric safety in her thinking.	

Item	EEA	USA
Container / closure system / delivery device	The use of a different container or closure system as the reference medicinal product uses is possible; provided that its potential impact on the biosimilar´s safety and efficacy is appropriately justified. In contrast to the FDA guidance document the EMA guideline does not further detail the topic.	The FDA may accept slight deviations in the design of a delivery device, or container closure system between the compared products. This is accepted by the FDA when certain defined conditions are met. If the proposed product is an interchangeable product, the FDA also reviews if the differences between the biosimilar and the reference product influence any critical design attributes, product performance, etc., or require additional use instructions. Thus, the FDA may require additional performance data for the delivery device or container closure system. Additional testing for leachables under stress- and under real time storage conditions should be performed for each product and its storage container.
Comment	Differences exist. The FDA requirements are stricter and the FDA guidance document provides more details.	

Item	EEA	USA
Postmarketing surveillance	To ensure the safety and efficacy of biological products, post-approval safety monitoring programs and continued benefit-risk assessment described in a risk management plan are important. The risk management plan should consider and address potential risks identified with the reference product. From significant importance is the comparison of the type, severity and frequency of the known adverse reactions of the biosimilar product and the reference product. Applicants should consider the possibility of additionally required post-approval surveillance; clinical studies or - trials such as post-authorization safety studies (PASS) or post-authorization efficacy studies (PAES). Regarding possible future substitutions of mAbs with biosimilar mAbs on national level, applicants should monitor the developments regarding that topic and should address it within the risk management plan.	A robust post-approval safety monitoring program and risk evaluation and mitigation strategies are crucial to ensure the safety and efficacy of biological products. The safety monitoring program should be designed in that way that a differentiation between adverse events of reference and proposed product is possible, including any new side effects not observed with the reference product in the past. Sponsors should also consider the possibility of additional post-approval surveillance, clinical studies or – trials.
Comment	No major differences exist. The FDA encourages the applicants to discuss the intended pharmacovigilance system with the agency.	

Item	EEA	USA
Quantity and type of scientific guidance documents for biosimilar products	Various product-class specific scientific guidance documents are available. One product-specific document for biosimilar mAbs available. Three overall guidance with similar content as the FDA overall guidance documents for biosimilar products (overall safety-relevant regulatory requirements, non-clinical- and clinical safety issues, quality considerations). No EMA guidance document available that specifically addresses the topic of clinical pharmacology data for biosimilar products.	No product-class specific biosimilar product guidance available. Seven FDA biosimilar products guidance documents, two of them procedural; five of them have an overall applicability similar to the EMA scientific guidance on biosimilar products (scientific/overall safety-relevant regulatory considerations, quality considerations, two Q&A documents, clinical pharmacology guidance). One guidance document addresses clinical pharmacology data for biosimilar products.
Comment	Differences exist in the quantity of available guidance documents. No significant differences exist between the available guidance documents regarding their quality, scientific contents and topics covered.	
Regulatory specifics	The EMA provides advice during scientific advice meetings.	The FDA encourages the sponsors to discuss their planned biosimilar development program and all significant stages/plan early with the FDA. The FDA reserves the right to determine type, amount and necessity of non-clinical and clinical testing, including immunogenicity data on a case by case basis in order to sufficiently demonstrate biosimilarity.
Comment	Differences exist. The FDA is involved in the biosimilar development program and thus, in the application process at a very early stage and following may better understand the specifics of the proposed biosimilar product and as a consequence, can request additional data in a tightly focused way. Applicant and FDA cooperate together.	
Non-clinical considerations		
Approach in order to assess biosimilarity	Totality-of-Data	Totality-of-Evidence

Item	EEA	USA
Comment	No differences.	
Approach to developing data demonstrating biosimilarity	Stepwise Depending on the level of evidence achieved in the structural and functional characterization, subsequent non-clinical and clinical studies are necessary to conduct more or less extensively.	Stepwise, target-orientated The sponsor should evaluate the extent of residual uncertainties regarding biosimilarity after each step and should address these uncertainties in the next step. The approach facilitates a target-oriented approach to non-clinical and clinical studies.
Comment	No differences.	
Testmaterial for comparability exercise	Appropriate quantity of batches intended for clinical use and commercialization	Appropriate quantity of lots intended for clinical use and commercialization
Comment	No differences.	
Steps of the non-clinical comparability program	(1) Extensive and robust structural and functional characterization (2) animal data including toxicity assessment	(1) Extensive and robust structural and functional characterization (2) animal data including toxicity assessment
Comment	No differences.	

Item	EEA	USA
Animal immunogenicity data	Immunogenicity assessment is considered as integral part of the comparability program. However, animal immunogenicity studies are not adequate to detect potential immune reactions to protein products in human individuals. Nevertheless, such study data may help interpreting in-vivo animal data and blood samples should be taken and banked.	Immunogenicity assessment is considered as integral part of the comparability program. Animal immunogenicity studies are not adequate to detect potential immune reactions to protein products in human individuals. Nevertheless, differences in manufacturing between the compared products may lead to varied immunogenicity and therefore anti-protein antibody response measurements in animals could give helpful information.
Comment	Slight difference regarding the purpose of animal immunogenicity studies. The FDA considers such data as useful when differences in manufacturing are to investigate.	
Non-clinical safety pharmacology, reproductive and developmental toxicity, carcinogenicity studies	Not necessary	Not necessary
Comment	No differences.	
Clinical considerations		
Evaluation approach	Totality-of-Data	Totality-of-Evidence
Comment	No differences.	
Testing approach to clinical evaluation	Stepwise	Stepwise, progressive
Comment	No differences.	

Item	EEA	USA
Testmaterial for clinical data generation	Ideally, clinical study data should be generated with biosimilar products derived from the commercial manufacturing process.	Ideally, clinical study data should be generated with biosimilar products derived from the commercial manufacturing process.
Comment	No differences	
Steps of the clinical comparability program	(1) Comparative human pharmacokinetic studies (PK) (2) Comparative human pharmacodynamic (PD) studies and clinical immunogenicity assessment (3) Clinical efficacy and safety trial(s), and when necessary confirmatory PK / PD trials	(1) Comparative human pharmacokinetic studies (PK) (2) Comparative human pharmacodynamic (PD) studies and clinical immunogenicity assessment (3) Clinical efficacy and safety trial(s), and when necessary confirmatory PK / PD trials
Comment	No differences.	
Extrapolation of immunogenicity findings for one condition of use to other conditions of use	Extrapolation of immunogenicity data from the confirmed indication or condition of use to other uses of the reference product should be justified; additional data may be required in certain cases.	Extrapolation of immunogenicity data for one condition of use to other conditions of use should be justified for each additional indication that is sought. The sponsor should use an adequately sensitive study population and treatment scheme in order to prognosticate distinctions in immune reactions between the comparators across the indications.
Comment	Differences exist. The EMA may require additional data.	
Extrapolation of clinical data across indications	Possible, when scientifically justified. Additional data may be necessary in certain cases	Possible, scientific justification for each additional indication that is sought is required Recommendation to study that indication that is sensitive enough to reveal clinically meaningful differences between the comparators.

Item	EEA	USA
Comment	Differences exist. The EMA may require additional data. FDA recommends studying that indication that is sensitive enough to reveal clinically meaningful differences. That poses a risk that immunogenic potential remains undetected in various indications.	
Immunogenicity studies	Pre- and post-approval Risk based approach	Pre- and post-approval Risk based approach
Comment	No differences.	
Pharmacokinetic data	Comparative PK- studies typically represent an essential part in demonstrating biosimilarity and should normally being provided. The selected PK parameters should be predefined and including their limits scientifically justified.	Comparative PK- studies typically typically represent a critical part of demonstrating biosimilarity, and usually, FDA expects the results of comparative human PK and PD studies to demonstrate biosimilarity. The selected PK- parameters and selection criteria should be predefined and scientifically justified.
Comment	No differences	
Pharmacodynamic data	The choice of PD-markers used in relevant studies should depend on their ability to demonstrate the intended clinical result. PD-measures should be performed within (together with) PK-studies where possible.	The selection of PD-parameters should be orientated on the relevance to clinical outcomes. PD-measures should be performed within (together with) PK-studies where possible.
Comment	No differences.	

Item	EEA	USA
PK/PD-study design	Comparable cross-over study design (products with short half-life) or comparable parallel study design (products with a long half-life)	Comparable cross-over study design (products with short half-life) or comparable parallel study design (products with a long half-life)
Comment	No differences	
PK-/PD- study alternative dosing scheme	Not provided	Possible under certain conditions and if properly justified
Comment	Differences exist. In certain cases, the FDA allows an alternative dosing scheme.	
Skipping of studies	A confirmatory clinical study may be unnecessary in cases where the data from the structural and functional characterization as well as data from the PK- and/or PD-profile are able to clearly demonstrate similar efficacy and safety, providing that the impurity- and excipients profiles are acceptable.	If the outcomes of the comparative human PK- / PD-studies show a meaningful correlation between PK- / PD-results and clinical effectiveness, comparative efficacy studies may be skipped.
Comment	Differences exist. The EMA also requires an acceptable impurity and excipients profile when it is intended to skip a trial.	
Length of follow-up period (Immunogenicity assessment)	One year at minimum for chronically administered products, Shorter periods may be possible when justified	One year at minimum for chronically administered products
Comment	Differences exist. Shorter periods may be possible with the EMA when this is justified.	
Comparative clinical study design	Comparable equivalence trial design, comparable margins should be statistically and clinically pre-specified and justified by using the reference product data	Comparable equivalence trial design with symmetric inferiority and superiority margins
Comment	No differences in trial design.	

Item	EEA	USA
Comparative clinical study sample size and duration	Sample size may vary due to dependency on prior non-clinical testing and PK-/PD- studies but should be adequate enough to allow the detection of differences between the compared products.	Sample size may vary due to dependency on prior non-clinical testing and PK-/PD- studies but should be adequate enough to allow the detection of clinically meaningful differences between the compared products; otherwise separate investigation of safety signals is required
Comment	No differences.	
Quality considerations		
Submission of comparative and similarity data	EMA does not encourage the applicant to submit these data prior submission of the final application dossier but some open items may be discussed during scientific advice meetings.	FDA encourages the applicant to submit these data at an early stage of development
Comment	Differences exist. The FDA is involved in the approval process at a very early stage of the biosimilar product development program.	
Stability	Stability data cannot be extrapolated from the reference product.	Requires that stability testing should include accelerated and stress testing as well as forced degradation studies; conducted under multiple stress conditions.
Comment	Differences exist as the FDA guidance document provides more detailed information.	
Handling of differences in impurity profiles between compared products	Documentation and proper justification of identified impurities with regard to their potential risks.	If differences in impurity profiles of the two products are detected, their potential impact to the product safety and efficacy should be discussed and supported with relevant data.
Comment	Differences exist. The FDA requires additional data.	

Item	EEA	USA
Differences in formulation and / or container closure system / delivery device	The impact of the different formulation and / or container closure system to the products safety and efficacy should be properly justified.	Additional data may be required to sufficiently rationale why the deviation does not affect the safety and efficacy of the biosimilar product.
Comment	Differences exist. The FDA may require additional data.	
Proposed shelf life	Requires that the proposed shelf life of the biosimilar product should be supported with full stability data. Comparative real-time, real-condition stability studies between the compared products are considered not necessary.	Real time data and real-condition stability data should support the proposed shelf life of the biosimilar product.
Comment	Differences exist. FDA and EMA have different meanings if real time data and real-condition stability data should support the proposed shelf-life.	
Re-demonstration of biosimilarity after marketing approval	Not required by regulations	Not addressed
Comment	No differences.	

Executive Summary

Innovative biological medicinal products have the potential to significantly improve a patient's life. Their market access is highly regulated in the EU and in the USA with very high safety requirements. When patents of the first original biological products reach their expiration date, the cheaper biosimilar products are in the process of obtaining marketing approval in order to compete against the innovator biological products.

What safety relevant standards are established for biotechnology-derived biosimilar products in both the European Union (EU) and the USA? And, is there potential to improve the current safety standards? The applicable scientific guidance documents for biosimilar products issued by the European Medicines Agency (EMA) and the US-American Food and Drug Administration (FDA) were analyzed and compared with respect to their safety requirements.

No major differences between the EU and the USA were identified with respect to the overall regulatory-safety standards that apply for biosimilar products established by the EU- / and US- law and as recommended in the scientific EMA- and FDA guidance documents.

Except of slight differences, the overall safety-related regulatory requirements required by legislation in the EU and the USA are very similar, including pharmacovigilance requirements. The FDA regulations (CFR) require stricter reporting (e.g., reporting of biological product deviations) and processing (e.g., prompt review of adverse events) than that required by the EU and the regulation of drug shortage is different in the two regions. By EU regulation, a minimum of one qualified person to perform certain safety-related tasks (e.g., batch compliance), the FDA does not require that position. Further, the EU legislation has established and implemented the black triangle labeling that represents extended monitoring of new and high-risk products; a comparable instrument is not implemented yet in the USA. While the US- law considers the determination of interchangeability this is not part of the EU legislation. And the law in both regions, the EU and USA, does not consider the re-demonstration of biosimilarity after a change to the manufacturing process occurs post-authorization.

While the US-law provides the FDA with more authority and power than the EMA is provided by Regulation (EC) No. 726/2004, the regulatory requirements established by EU-legislation provide the manufacturers with more individual responsibility (e.g., they are responsible to watch their distributors) than the US-law provides to the US-American medicinal product manufacturers. The main European legal document for medicinal products, Directive 2001/83/EC needs to be transposed into national law by the EU-member states while the United States Code applies without transposing into national law. In consequence, the EU-member states have more freedom regarding the implementation of the EU Directive into their national law.

Regarding the pharmacovigilance and postmarketing requirements in both regions, the EU and the USA, these are very similar for the last few years. In both regions, pharmacovigilance includes postmarketing studies, clinical trials, risk evaluation and risk mitigation strategies, patient registries and special labeling. Although

appropriate instruments to monitor and further confirm the safety and efficacy of medicinal drug products are available (e.g., postmarketing studies), their application is handled differently and on a case by case basis.

Regarding the regulatory burden and available scientific guidance documents, there are some differences between the EU and the USA. The regulatory burden in the EU is higher than in the USA due to the European- and national legislations and the required transformation of EU legislation into national law. The quantity of available guidance documents, in particular documents which address the specifics of individual product classes, is higher in the EU than in the USA. The scientific value, quality and content of the available scientific guidance documents regarding quality issues, non-clinical and clinical requirements as well as overall safety-related considerations to biosimilar products is high in both regions.

The scientific EMA- and FDA guidance documents concerning the quality, non-clinical and clinical safety requirements for biosimilar products are very similar and comparable. The scientific content of the documents is mostly the same, but there are small differences (e.g., better explanations, examples) that make the FDA documents clearer and more meaningful.

The most significant differences between the two regions, EU and USA, that were identified in the scientific guidance documents and which belong to the safety of biosimilar products are related to the: [1] determination of interchangeability; [2] automatic substitution of biosimilar products; [3] pediatric assessment requirement; [4] the extrapolation of safety and efficacy data including immunogenicity data across indications; and [5] testing requirements when using a different container closure or delivery device system.

Veröffentlichungen

06/2017	Veröffentlichung der Publikation „Sicherheitsstandards für Biosimilars in europäischen und US-amerikanischen Leitlinien“ in Heft 6/2017 der „pharmind“