Biosimilars in the U.S.
- the long way to their first approval

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List of Abbreviations

AAC	Arthritis Advisory Committee
aBLA	abbreviated Biologic License Application
ADA	Anti-Drug Antibody
ANC	Absolute Neutrophil Count
ATMPs	Advanced Therapy Medicinal Products
AUC	Area under the Curve
AUEC	Area under the Effect Curve
BLA	Biologic License Application
BPCI	Biologics Price Competition and Innovation
BPD	Biosimilar Biologic Product Development
BsUFA	Biosimilar User Fee Act
CAR	Chimeric Antigen Receptor
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CTD	Common Technical Dossier
EMA	European Medicine Agency
EU	European Union
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
G-CSF	Granulocyte-Colony Stimulating Factor
HCT/Ps	Human cells, tissues, or cellular or tissue-based products
ICH	International Council for Harmonisation
IND	Investigational New Drug
MA	Marketing Authorization
MAA	Marketing Authorization Application
MIU	Million International Units
MoA	Mode of action
NDA	New Drug Application
OCTGT	Office of Cellular, Tissue, and Gene Therapies
ODAC	Oncologic Drugs Advisory Committee
PBPC	Peripheral Blood Progenitor Cell
PD	Pharmacodynamic
PDUFA	Prescription Drug User Fee Act
Ph.Eur.	European Pharmacopoeia
PHS Act	Public Health Service Act
PK	Pharmacokinetic
QTPP	Quality Target Product Profile
rG-CSF	recombinant Granulocyte-Colony Stimulating Factor

rhG-CSF	Recombinant human Granulocyte-Colony Stimulating Factor
ROI	Return-on-investment
U.S.	United States
w/o	without

1. Executive Summary

The first biosimilar approval in the United States (U.S.) has been awaited for a long time. Europe already started approving biosimilars in 2006. In contrast, in the U.S. the first biosimilar was only granted marketing authorization (MA) in 2015. This first abbreviated biologic license application (aBLA) was submitted to the FDA by Sandoz seeking licensure in the U.S. for their filgrastim going by the brand name Zarxio and can be regarded as a model case for the biosimilar approval process in the U.S. because neither guidance documents were published nor the regulatory aBLA pathway was established at the time Sandoz started their development program of Zarxio. The FDA had the opportunity to learn from this aBLA and to define and optimize their requirements for submission of an aBLA. This learning process is partly reflected in the finalized guidance documents published after the approval of the first biosimilar. Due to the ongoing learning process of the FDA while already assessing aBLAs, the publication of further guidance documents has been slowed down. There are key issues which the FDA still needs to decide on, e.g. extrapolation of data to indications of use which have not explicitly been tested in clinical trials and naming of biosimilars.

Comparing the approval process of Sandoz' filgrastim in the U.S. with the approval process in Europe reveals that the basic situation at the beginning of the development program was similar in terms of lacking finalized guidance documents and the lack of already approved biosimilars to learn from. Both procedures were of comparable duration. The main difference was the successive implementation of the procedures. Apparently the documentation submitted in the U.S. was more extensive than the European one, most likely due to improved test methods and additional "bridging studies" demonstrating high similarity of the European approved reference product, the U.S.-licensed reference product and the proposed biosimilar. It seems as if the FDA was more thorough in assessing the provided data than the EMA. Nonetheless, both agencies basically followed the same ideas which are reflected by the updated European guidelines of 2015 and the finalized U.S. guidance documents of 2015.

Looking at the ongoing biosimilar biologic product development (BPD) programs and the aBLAs already submitted to the FDA, more biosimilar approvals can be expected in the near future in the U.S.. However, due to patent protection and patent issues it might take some time until the next biosimilars are being placed on the market in the U.S..

Analyzing the potential causes for the delay of the approval of biosimilars in the U.S. revealed that there is no "one reason". Several points have to be considered which add up to delaying the whole process. First of all, the need for an abbreviated pathway for biosimilar approval was noticed later than in other countries, e.g. in Europe, and therefore, the process of establishing the legal basis for an abbreviated pathway started later in the U.S.. The "litigation culture" in the U.S. forces the FDA to create a more solid basis for the assessment of biosimilars for prevention of being sued,

supporting the cautious behavior of the FDA in publishing finalized guidelines and approving biosimilars. In addition, the following issues contribute to the delay of biosimilar approval:

- the so-called “patent dance”
- internal and external discussions about the acceptability of extrapolation of data to indications of use which have not explicitly been tested in clinical trials
- defining the requirements for interchangeability/substitution of biosimilars
- the immunogenicity potential of biosimilars which might impact the safety of the product
- the “Nonproprietary Naming of Biological Products”

Some of these issues have yet to be resolved. Additional approved aBLAs will be required until the FDA will have finally defined the assessment process for biosimilars fully. The FDA will need to publish additional guidance documents during their learning process which will clarify their view on the outstanding issues and might affect the future of biosimilars and the abbreviated biologics license pathway according to 351(k) of the PHS Act in the U.S..

2. Introduction

Biosimilars are biological medicinal products which are highly similar to an already approved biological reference product and can obtain licensure through an abbreviated pathway.

In March 2015, the first biosimilar, also called follow-on biologic, was licensed in the U.S.. This is surprisingly late compared to Europe, where since 2006, 22 biosimilars of six different product classes were approved, two of which were withdrawn, amounting to 20 licensed biosimilars to date [63]. Therefore, the question arises: Why did it take so much longer in the U.S. than in Europe to successfully approve biosimilars and what do we have to expect in the future in terms of biosimilars in the U.S.?

This thesis describes the basis for biosimilar approval in the U.S. by outlining the legal basis and the available guidance published by the FDA and looking into the approval process of Zarxio, brand name of Sandoz' filgrastim in the U.S. and the first U.S. biosimilar licensed in March 2015. It analyzes which aspects of the guidance documents are reflected in the application, even though the draft guidance documents were published rather late in the development program of this biosimilar. Furthermore, the approval process of Zarzio (brand name of Sandoz' filgrastim in Europe) is compared to the approval process of Zarxio in the U.S., outlining the European legal basis along with the guidance documents published at the time of approval. The prospects for further biosimilar licensures are presented. Finally, possible reasons for the delay of biosimilar approvals in the U.S. are discussed.

Following the discussion, the thesis concludes with an outlook on what can be expected for licensure of "Advanced therapeutic medicinal product-similars" in Europe and the U.S..

3. First biosimilar approval for filgrastim under 351(k) of the PHS Act in the U.S.

It has been a long way to the first biosimilar approval under section 351(k) of the PHS Act in the U.S. Finally, on 6th March 2015, a major milestone regarding biosimilars in the U.S. was reached when the MA was granted for Sandoz Inc.'s Zarxio [8] - a biosimilar to Amgen's Neupogen - originally approved in the U.S. in 1991, a filgrastim for treatment of cytotoxic chemotherapy induced Neutropenia, for treatment of patients suffering from cancer undergoing bone marrow transplantation, for treatment of patients undergoing autologous peripheral blood progenitor cell collection and therapy, and for treatment of patients with severe chronic neutropenia [77].

3.1. Regulatory Framework in the U.S.

Generic medicinal products can be approved by an abbreviated MA pathway since the Drug Price Competition and Patent Term Restoration Act of 1984 was adopted [83], commonly known as the "Hatch-Waxman Act" (refer to sections 505(b)(2) and 505(j) of the Federal Food, Drug, and Cosmetic Act (FDC Act)). As biological medicinal products are more complex in regards to e.g. structure, stability and manufacturing processes than small molecule drug products, a separate approval pathway was necessary, taking into account the complexity of those molecules. Finally, in 2010 the Public Health Service Act (PHS Act) was amended in section 351 by introducing an abbreviated licensure pathway under section 351(k) for biological products for which at least biosimilarity or even interchangeability is demonstrated in comparison to a biological reference product which has been approved by the FDA under 351(a) of the PHS Act. The Biologics Price Competition and Innovation (BPCI) Act, being part of the Patient Protection and Affordable Care Act (section 7001 - 7003), was enacted on 23rd March 2010 [81].

The BPCI Act lays down the legal basis for the "Licensure of biological products as biosimilar or interchangeable". In section 351(i) of the PHS Act (42 U.S. Code §262(i)) the terms "biological product", "biosimilarity", "interchangeability", and "reference product" are defined [81].

Accordingly, a "biological product" is "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" [81].

"Biosimilarity" means "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product" [81].

A biological product can be deemed “interchangeable” to a reference product in case it is determined to be “biosimilar to the reference product; and it can be expected to produce the same clinical result as the reference product in any given patient. [Furthermore,] the risk in terms of safety or diminished efficacy of alternating or switching between 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. [Then,] the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product” [81].

A “reference product” is defined as “the single biological product licensed under subsection 351(a) of the PHS Act against which a biological product is evaluated in an application submitted under subsection (k) ” [81].

Section 351(k) of the PHS Act (42 U.S. Code §262(k)) lists the requirements concerning the marketing authorization application (MAA) [81], i.e.

- the required content which can be amended in case the FDA considers certain data to be superfluous for assessment
  - “Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
  - Animal studies (including the assessment of toxicity); and
  - A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.” [81]
- the requirements for determination of interchangeability [81]
- prerequisites concerning the reference product [81]
- regulations in terms of data/market exclusivity for the first interchangeable biologic product and for the reference product [81]
- provisions for preparation of guidance documents by the FDA [81]

Furthermore, section 351(l) of the PHS Act deals with handling of patent issues [81], including

- provision and handling of confidential information including timelines
- provision of lists and descriptions of patents
- handling patent disputes, infringements, and newly issued or licensed patents
- notice of commercial marketing and preliminary injunction
- limitation on declaratory judgment action [81]

In addition, the BPCI Act amends Section 505(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S. Code § 355c - Research into pediatric uses for drugs and biological products) and specifies that

a biosimilar biological product shall be considered to have a new active ingredient with regards to the requirement for conducting clinical studies in pediatric populations [81]. In contrast, "an interchangeable biologic product" does not have a new active ingredient and therefore does not require additional studies in pediatric populations [81]. The provisions regarding pediatric studies of biological products including provisions for market exclusivity are specified in section 351(m) of the PHS Act (42 U.S. Code § 262) as amended by the BPCI Act [81].

The BPCI Act also emphasizes that all biologics have to seek licensure through 351 of the PHS Act as amended. However, exceptions are laid down for products where a biological product of the same product class has previously been licensed under 505 FD&C Act (21 U.S. Code § 355) until the date of enactment of the BPCI Act. For these biological products, the applicant may file an application under 505 FD&C Act within the next 10 years from enactment of the BPCI Act. That does not apply to biological products where a potential reference product had already received licensure under 351(a) of the PHS Act. 10 years after enactment of the BPCI Act, all biologics previously approved under the 505 FD&C Act shall be deemed to be licensed under 351 of the PHS Act (section 7002(e) of the BPCI Act) [81].

According to the Prescription Drug User Fee Act (PDUFA), the BPCI Act laid down that the FDA "shall develop recommendations regarding a new user fee program for biosimilars submitted under 351(k) of the PHS Act for the Fiscal Years 2013 to 2017 to present to Congress" [81] .The developmental process should include consultations with different stakeholders such as the "Committee on Health, Education, Labor, and Pensions of the Senate; the Committee on Energy and Commerce of the House of Representatives; scientific and academic experts; health care professionals; representatives of patient and consumer advocacy groups; and the regulated industry" [81]. Following the recommendations proposed by the FDA to the Congress on January 13th, 2012, the Congress (set deadline by BPCI was January 15th, 2012) was asked to establish a program for collection of user fees not later than October 1st, 2012 [81]. Finally, "The Biosimilar User Fee Act (BsUFA)" as part of the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed by the President of the United States on July 9th, 2012 [10].

The primary goal of the BsUFA is to enable the FDA to collect fees with regards to biosimilar MAA covering for the workload before aBLA submission and during the review process to improve and accelerate the review process of MAA by the FDA [34, 82]. The BPD program was established as part of the BsUFA [82]. The legal basis for the BPD fees (21 U.S. Code §379j–52) was laid down by the BsUFA. Every sponsor either submitting an investigational new drug application (IND) for clinical trials testing a potential biosimilar or requesting advice from the FDA regarding their biosimilar development program, i.e. requesting a BPD meeting, automatically takes part in the BPD program resulting in the payment of the required fees (refer to Table 1) [29, 82].

Table 1 lists the fees applicable to all applications planned or filed under section 351 of the PHS Act (42 U.S. Code §262) during the Fiscal Year 2016 [29].

Table 1 Fiscal Year 2016 BsUFA Fees (Data obtained from the official FDA homepage [29])

BPD	Initial	$237,420
	Annual	$237,420
Application	with Clinical	$2,374,200
	w/o Clinical	$1,187,100
Supplement	with Clinical	$1,187,100
Product		$114,450
Establishment		$585,200
Reactivation		$474,840

As outlined for the first BsUFA, a time consuming process is required to enact the law. Therefore, public consultation for reauthorization of BsUFA (BsUFA II) for Fiscal Years 2018 through to 2022 has already started on 18th December 2015 [32].

3.2. Guidelines

After the abbreviated pathway was legally established and finally enacted, many questions were left open regarding which data, analyses, and studies had to comprise an application package to receive regulatory approval by the FDA. The law left a lot of design possibilities for implementation of the aBLA which had to be discussed, developed, and defined by the FDA involving the public, resulting in guidance documents for industry. Detailed guidance was missing until 2012 when the first and long awaited “draft guidelines” were published by the FDA. Although the issuance of guidance by the FDA was not a prerequisite for the FDA to assess an application submitted under 351(k) of the PHS Act [81], no application was submitted before 2014 (refer to section 5.). Guidance documents are not legally binding for sponsors. However, if uncertainties about the required documentation occur and if the sponsor favors different approaches than proposed by the FDA’s guidance documents, the sponsor should seek advice from the FDA and discuss their approach with the FDA early during the development process [51].

Table 2 Guidelines regarding biosimilar biologic products published by the FDA

TOPIC	DRAFT	FINAL
Scientific Considerations in Demonstrating Biosimilarity to a Reference Product	February 2012	**April 2015**
Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product	February 2012	**April 2015**
Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 Guidance for Industry	February 2012	**April 2015**
Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants	March 2013	**November 2015**
Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product	May 2014	*pending*
Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act	August 2014	*pending*
Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009	May 2015	*pending*
Nonproprietary naming of biological products	August 2015	*pending*
Considerations in Demonstrating Interchangeability to a Reference Product	*planned [94]*	
Labeling for Biosimilar Biological Products	*planned [94]*	
Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity	*planned [94]*	

Table 2 gives an overview of all guidance published by the FDA to date. The first four guidelines are already finalized, four draft documents are available and three more guidelines were announced to be prepared and published in the near future [94].

The content of the first three draft guidelines has already been described in detail in the master thesis of E. Baldyga in 2012 [5]. To outline the main aspects of the draft guidance documents which were available at the time of submission of the aBLA for Zarxio, a summary of these draft guidelines is provided below listing the main aspects and amendments which were described and introduced in the final documents:

1) The basic guidance on the requirements for biosimilar applications is provided in "**Scientific Considerations in Demonstrating Biosimilarity to a Reference Product**" [51]:

The FDA advises the sponsor to follow a **"stepwise approach"** in developing a follow-on biologic. The stepwise approach is recommended because the extent of structural analyses and the subsequent study design e.g. for *in vitro* and *in vivo* PK/PD studies, toxicity testing, and clinical immunogenicity and safety studies depends largely on the **"residual uncertainty"** regarding biosimilarity of the biosimilar and its reference product**.** However, the finalized guidelines qualify this position and state that certain "investigations could be performed in parallel" [51].

The FDA considers the **"totality of evidence"** before concluding on the outcome of the assessment of an aBLA. Even if differences are determined between the follow-on biologic and the reference product, e.g. post-translational modifications with no clinical impact, the FDA is going to look at the totality of evidence using a "risk-based approach", i.e. considering the likelihood for a clinical impact with regards to safety or efficacy of the observed difference, to conclude on the biosimilarity demonstrated by the sponsor [51].

When a non-U.S.-licensed reference product is used in the clinical studies, **"bridging studies"** always have to comprise data from analytical studies to demonstrate biosimilarity of the proposed product with the non-U.S.-licensed as well as with the U.S.-licensed reference product. In addition, bridging studies demonstrating the PK/PD similarity are most likely recommended to be included in the submission package [51].

This guidance describes the basic principles for conducting the required analyses to demonstrate biosimilarity of the follow-on biologic and its reference product including "comparative structural analyses, functional assays, animal testing, human PK and PD studies, clinical immunogenicity assessments, and comparative clinical studies" [51]. Regarding structural analyses, a new paragraph was introduced pointing out that in case the manufacturing process changes during the development process, the product prior to and after the change has to be thoroughly characterized. The extent of further studies highly depends on the extent of detected changes to the structure [51].

Regarding animal toxicity studies, the finalized guideline contains some new views and clarification on the necessity of these studies. The guidance underlines that the benefit of the test for the totality of evidence has to be carefully considered. If scientifically sound data with regards to safety is

available from clinical studies using the same proposed product with the same formulation and same proposed route of administration, the animal studies might be waived. In addition, it is recommended to consider further *in vitro* tests using human cells or tissues instead of animal studies in case it is scientifically justified that the animal studies are not needed. Immunogenicity studies in animals are not meaningful with regards to human immunogenicity. However, they can be used as supportive data to demonstrate biosimilarity or to reveal differences between the follow-on biologic and its reference product [51].

It is mandatory to provide PK, and PD studies and immunogenicity assessment in humans. It was newly introduced in the finalized guideline that if these studies do not leave any residual uncertainty about biosimilarity of the follow-on biologic and its reference product, further comparative analyses could be waived. The studies in humans analyzing PK, PD, and immunogenicity can be regarded as being of core importance for the aBLA as they will reveal clinically meaningful differences. It is stressed that the immunogenicity of a medicinal product is of major importance with regards to safety and efficacy. Therefore, the immunogenicity profile of the proposed product in comparison to its reference product is of pivotal interest and cannot be fully shown by *in vitro* or animal studies. A comparative parallel design in treatment-naive patients is recommended by the FDA to analyze immunogenicity. The population and treatment regime have to be chosen carefully to be "adequately sensitive for predicting a difference in immune response between the proposed product and the reference product" [51] to allow for extrapolation across all conditions of use.

Extrapolation is addressed separately as different requirements have to be fulfilled to allow for it. For example, the mode of action (MoA) has to be known for each of the conditions of use for which licensure is sought. It is newly introduced in the finalized guideline that if there are differences regarding the prerequisites of extrapolation between conditions of use, extrapolation does not have to be precluded automatically. Thorough scientific justification always has to be provided by the applicant in terms of extrapolation [51].

Post-marketing measures should include studies to reveal adverse events which have not been detected yet due to the relatively small numbers of patients included in the clinical trials, especially adverse events not yet associated with the respective reference product [51].

2) The guidance on "**Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product**" [48] provides information on which data is required for submission of an aBLA in terms of Chemistry Manufacturing and Controls (CMC) in more detail than the general guidance document "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" [51]. Guidance is given regarding the "Expression System", the "Manufacturing Process", the "Assessment of Physicochemical Properties", the "Functional Activities", the "Receptor Binding and Immunochemical Properties", the "Impurities", the "Reference Product and Reference Standards", the "Finished Drug Product", and the "Stability"

[48]. In general, guidance documents published by the International Council for Harmonisation (ICH) should be followed [48].

Some main points of the guidance on "Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product" [48] to be considered are outlined below:

A complete CMC data package as required under 351(a) of the PHS Act is required to be submitted under 351(k) of the PHS Act. Furthermore, comparability data is substantial. The sponsor should always use state-of-the-art analyses. However, the limitations of each method to reveal any differences of the proposed product and the reference product have to be well understood by the sponsor to apply the most suitable and the most sensitive method to detect any differences. The chemical, physical, and biological characterization constitute the basis for the extent of required subsequent studies as they largely depend on the remaining residual uncertainties in terms of biosimilarity of the proposed product and the reference product and therefore, this data should be discussed with the FDA early in the development process before starting *in vivo* studies [48]. A new introduction to the finalized guideline is the recommendation to test an adequate number of batches to reveal the lot-to-lot variability of the follow-on biologic and the reference product. Furthermore, it was added that multiple functional assays should be performed to demonstrate biosimilarity [48]. Regarding impurities, it is newly introduced that especially the process-related impurities might differ between the follow-on biologic and the reference product. However, these differences should be analyzed carefully by considering a risk-based assessment [48]. With regards to stability data, accelerated, stress stability and forced degradation studies as well as sufficient real-time and real-condition studies have to be conducted with the follow-on biologic and the reference product to compare degradation profiles [48].

Another, already finalized guideline is the guidance document regarding "**Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants**" [46].

According to the BsUFA, a performance goal includes meeting management goals which have to be met by the FDA [82]. The different meeting types outlined in this guideline should be requested by the sponsor during the development of their biosimilar to obtain guidance from the FDA to improve and accelerate their submission of an aBLA [46]. Five different meeting types can be requested by the sponsor - each applicable under certain provisions (does not preclude sequential meeting requests; Type 2 and 3 meetings can be requested as often as required; provisions are made for one Type 1 and Type 4 meeting each) [46]:

1. Biosimilar Initial Advisory meeting: - general discussion about feasibility of licensure under section 351(k) of the PHS Act for a specific product

Required data for meeting request:

- "preliminary comparative analytical similarity data from at least one lot of the proposed biosimilar biological product compared to the U.S.-licensed reference product" [46]

- overview of the proposed development program (planned studies) including summary of findings of all completed studies [46]

2. BPD Type 1 meeting: - necessary for an otherwise stalled BPD program to proceed, e.g. after receipt of complete response letter from the FDA to discuss the approach on how to address the outstanding issues [46]

3. BPD Type 2 meeting: - "discussion of a specific issue (e.g., proposed study design or endpoints) or questions where the FDA will provide targeted advice regarding an ongoing BPD program" [46]

- may include substantial review of summary data - no complete study data will be reviewed [46]

4. BPD Type 3 meeting: - in-depth data review and advice meeting regarding an ongoing BPD program [46]

- review of full study reports or analytical similarity data as planned to be submitted in the aBLA [46]

- updated development plan should be provided [46]

5. BPD Type 4 meeting: - discussion of format and content of a biosimilar biological product application or supplement to be submitted under section 351(k) of the PHS Act (excluding full review of data or study reports → refer to Type 2 meeting) [46]

The detailed meeting procedure including requesting, granting, rescheduling, cancelling of the meeting is described in the respective guidance document [46].

Guidance on the required design of clinical pharmacology studies was missing until May 2014 when the draft guidance document "**Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product"** was published [50]. The main aspects are outlined below:

Clinical pharmacology studies are a core element in demonstrating biosimilarity of the follow-on biologic and its reference product. These studies comparing the PK- and PD-profile of the analyzed products represent the basis for justification of extrapolation to additional conditions of use if similarity can be demonstrated [50].

As already mentioned above, residual uncertainties impact the extent of clinical studies needed which also depend on the ability to address these outstanding uncertainties, and the ability to reveal differences [50].

When assessing PD and PK of the follow-on biologic and its reference product, the endpoints should be chosen carefully and guidance is given regarding which aspects to consider when choosing suitable PD markers [50].

The outcome of the comparative analytical characterization of biosimilarity may lead to the following classifications which impact on the extent and design of the subsequent clinical studies (stepwise approach): 1. highly similar with fingerprint like similarity, 2. highly similar, 3. similar, or 4. not similar [50].

It is of great importance that "the bioanalytical methods used for PK and PD evaluations are accurate, precise, specific, sensitive, and reproducible" [50].

When analyzing PK and PD, three assay types are listed to be of major importance during the development program: 1. ligand binding assays, 2. concentration and activity assays, and 3. PD assays. These assays are described in detail [50].

The similarity of safety and immunogenicity of the proposed product and the reference product is another core issue during the BPD program. Immune-mediated toxicity and/or lack of effectiveness should be analyzed during the clinical pharmacology studies. However, additional analyses pre- or post-approval are encouraged as stated by the FDA. If differences in the safety or immunogenicity profile are observed - depending on the extent - the further BPD for this product under 351(k) of the PHS Act should be questioned [50].

The study design of the clinical pharmacology studies should be discussed in detail with the FDA. A crossover design is favored in case of short half-life of the product. In case of long half-life of the proposed product or signs of immunogenic potential are observed, a parallel design is recommended by the FDA [50].

It is made clear that at least one clinical PK and, if appropriate, a PD study must include an adequate comparison of the follow-on biologic to the U.S.-licensed reference product. In case a non-U.S.-licensed reference product is used in some supportive studies, bridging studies are necessary which are mainly analytical, comparing all three products with each other and in addition PK and PD studies might be supportive or even required which should be discussed with the FDA [50].

Regarding the study population, PK/PD analyses are preferable to be conducted in healthy volunteers. If a healthy study population is not appropriate, i.e. immunogenicity, toxicity or PD marker are only assessable in patients, the study should be conducted in patients. The choice of demographic group has to be justified by the sponsor [50].

The tested dose should be selected according to a few recommendations. In patients, the approved dose of reference product is regarded to be appropriate. In healthy volunteers or when PD is determined, a lower dose in a steep part of the dose-response curve should be selected. In case of non-linear correlation of the dose-response, a dose range might be appropriate for testing [50].

It is recommended that the same route of administration is used as the reference product received licensure for. In case more than one route is available, the most sensitive route should be selected [50].

Recommendations for appropriate PK/PD measurements are provided. For example, PK should be assessed by determining AUC and C_{max}. The PD endpoint(s) have to be chosen carefully. "Comparison of the PD marker(s) between proposed biosimilar product and the reference product should be by determination of the area under the effect curve (AUEC)" [50]. The duration and suitable time points for measurement will depend on the respective PD marker(s) [50].

The clinical pharmacology similarity is analyzed by statistical methods (referring to the Guidance on "Statistical Approaches to Establishing Bioequivalence" [40]). Three prerequisites are listed: 1. a criterion to allow the comparison, 2. a confidence interval, in general 90%, for the criterion, and 3. an acceptable limit, proposed 80 - 125% [50]. In case the PD or PK values do not lie within the acceptance range implying difference, the sponsor has to scientifically justify the clinical insignificance for safety, purity and potency of the product [50].

3.3. Approval process for Zarxio

3.3.1. Timeline of the approval process for Zarxio

It looks like a long time from establishing the legal basis for an abbreviated pathway for biosimilar approval in 2010 [81] until the first biosimilar approval in 2015 [8]. However, behind the scenes the developmental process for submission of a MAA has been on its way for a long time. Table 3 lists the timetable for some key dates during preparation and submission of the MAA of Zarxio as well as the final approval date.

Table 3 Overview of the timeline for MAA and approval of Zarxio in the U.S. (*italic font represents legal framework*)

Date	**Activity**
October 1st, 2009	Type B meeting* for discussion of 351(a) pathway for Zarxio licensure
March 23rd, 2010	*BPCI Act enacted, establishment of 351(k) pathway (aBLA)*
October 11th, 2010	Type B meeting (Pre-IND meeting)* for discussion of 351(k) pathway for Zarxio licensure
November 1st, 2010	Submission of study design for pivotal trials #302 and #109
April 4th, 2011	Feedback from agency regarding proposed study design
April 2012	*First draft guidelines published*
November 19th, 2013	BPD Type 4 meeting
May 8th, 2014	Submission of MAA to the FDA
May 23rd, 2014 - March 5th, 2015	30 amendments were submitted to the agency during review period
January 7th, 2015	Oncologic Drugs Advisory Committee Meeting
March 6th, 2015	MA granted
April 2015	*First finalized guidelines published*

Dates retrieved from references [8, 74, 78]

* Type B meetings [43]: e.g.

- Pre-investigational new drug application (pre-IND) meetings (21 CFR 312.82)
- Certain end-of-phase 1 meetings (21 CFR 312.82)
- End-of-phase 2 and pre-phase 3 meetings (21 CFR 312.47)
- Pre-new drug application/biologics license application meetings

The timeline reveals that Sandoz had already planned on submitting a MAA for Zarxio before the abbreviated licensure pathway for biosimilars was even created. After obtaining a license for Zarzio

in Europe in February 2009 [63], Sandoz requested a Type B meeting for discussion of submitting a standard biologic license application (BLA) under 351(a) of the PHS Act because the abbreviated pathway was not yet established [78]. However, as soon as the pathway was enacted on March 23rd, 2010, Sandoz took the opportunity to request a meeting with the FDA to discuss the possibility to submit an aBLA under 351(k) of the PHS Act. This meeting was held in October 2010 [78]. The study design for the pivotal studies which included the U.S.-licensed reference product as comparator was submitted a month later. However, the agency did not responded until five months later in April 2011 [78]. The efficacy study EP06-302 (PIONEER) comparing the proposed product to the U.S.-licensed reference product was started in December 2011 as listed in the publicly accessible clinical trials database of the U.S. (https://clinicaltrials.gov) [76]. As the first draft guidance documents were only published in 2012, Sandoz had to rely on guidance obtained during meetings with the FDA discussing the analyses and studies required for licensure approval. The final BPD type 4 meeting in preparation of the actual submission package was held in November 2013 [74]. This was the first meeting requested by Sandoz in accordance with the guidance on "Formal meeting between the FDA and Biosimilar Biological Product Sponsors or Applicants" [46], because the draft guideline was only published in March 2013 (refer to Table 2) outlining the different meeting types which can be requested at the FDA to receive guidance on the BPD program. Finally, the FDA received their first aBLA under 351(k) of the PHS Act on May 8th, 2014 submitted by Sandoz [35]. Eight months after submission took place and after several amendments were submitted to the agency, the Oncologic Drugs Advisory Committee (ODAC) met on January 7th, 2015 voting unanimously for recommendation of granting MA to Zarxio for all indications licensure was sought for [13]. Licensure was finally granted on March 6th, 2015 [35] - 10 months after submission of the first aBLA - meeting the performance goal under the BsUFA to review and approve 70 % of all aBLA submitted during the Fiscal Year 2014 within 10 months time [33].

3.3.2. Summarized results comprising aBLA for Zarxio

As outlined before, it is not the aim of a follow-on biologic to be 100% identical to its reference product. Due to the complex structure and the biological manufacturing process, the follow-on biologic is not identical but highly similar to its reference product. Therefore, differences can be detected during analytical, non-clinical and clinical comparison of the proposed product and its reference product but these differences are not allowed to have a significant impact on the clinical efficacy or safety of the proposed product. The 'totality of evidence' must allow for the conclusion that similarity has been fully demonstrated [51].

The following analyses and studies were submitted to the FDA for review as part of the aBLA of Sandoz' filgrastim named Zarxio:

During the comparative analytical analyses of the proposed product (EP2006 corresponds to Zarzio in the European Union (EU) and Zarxio in the U.S., respectively), the U.S.-licensed reference

product (Neupogen), and the EU-licensed reference product (Neupogen), similarity has been described for the following aspects which represent the basis of the bridging studies [37, 65]:

- *Primary, secondary, and tertiary structure* of the proteins are highly similar [37].

- *Biological activity* of the proteins analytically show similarity which was analyzed by statistical equivalence testing. It has to be noted that the manufacturing process for EP2006 (filgrastim) was amended during the development program and therefore, the clinical trials were performed using the product prior to manufacturing changes - referred to as "clinical process" product and the product used after manufacturing changes is referred to as the "commercial process" product. These two products were combined for the statistical analysis of the biological activity assay as well as the data obtained for U.S. reference product in a vial or a pre-filled syringe, respectively [65].

- *Receptor binding* of the proteins is highly similar and it was concluded that the same MoA applies to all conditions of use listed in the application form. Slight differences in binding kinetics were observed depending on the different buffer systems. It was argued that this is unlikely to have an impact on the clinical outcome as the effect of the buffer system will be diminished by solvent conditions in the body [65]. The overall binding conditions were determined to be similar in all three analyzed products.

- Regarding *clarity and sub-visible particles* and *product-related substances and impurities,* comparative analyses revealed no significant differences and therefore, it can be concluded that the three products are highly similar [65].

- The comparative *stability studies* (long-term, accelerated, and stress conditions) indicated comparable degradation processes and products of the three analyzed products [65].

- When analyzing the *impurities and protein-related substances,* minor differences in N-terminal truncated variants were observed which are unlikely to have an impact on clinical outcome as the first 10 amino acids are not situated in the protein-structured region nor in the receptor-binding region [65], as well as minor differences in Nor-Leucin species which are product-related substances and are thought to not have an impact on immunogenicity or safety profile as demonstrated by respective comparative clinical studies [65]. Lower amounts of deaminated species were determined in EP2006. A lower amount is not critical for similarity of the products as these species are degradation products of Granulocyte-Colony Stimulating Factor (G-CSF) [65]. The observed differences in degradation products might result from differences in age of the products, non-linear kinetics of degradation process or the difference in buffer system and are not considered to have a clinical impact [65].

-When analyzing the *protein concentration* of the products, data revealed that the protein content of the EU-licensed reference product as well as the U.S.-licensed reference product was highly similar to the "clinical process" product of EP2006. However, statistical equivalence was lacking for the "commercial process" product of EP2006 in comparison to the U.S.-licensed product whose protein content was significantly higher than that of the "commercial process" product of EP2006 [37, 44,

65]. This was a major issue which was discussed in detail during the Advisory Committee meeting held in January 2015. Before the meeting took place, the FDA requested further information on this issue including additional batches for analyses as only six lots of the "commercial process" product had been analyzed and this was deemed to be of limited informative value for statistical analysis. Sandoz submitted data of three additional lots of "commercial process" product [44]. However, they admitted that in the first place data of only four instead of six independent lots had been provided. In addition, two more lots of the clinical drug product were provided. Therefore, seven lots of the "commercial drug product" and 13 lots of the clinical drug product of EP2006 were finally available for statistical analysis. The results did not show equivalence of the "commercial drug product" to either U.S.-licensed reference product or to the EU-licensed reference product. The FDA argued that n=7 of commercial drug product lots was too small for adequate statistical analysis. When combining the lots of the commercial with the clinical drug product (n=20, combination of commercial with clinical process acceptable as products are comparable) the test revealed equivalence to the reference products [44].

Immunogenicity is one of the main safety aspects to be considered when treating patients with biologicals. Therefore, the comparable immunogenic potential of the proposed product and its reference product is substantial for demonstrating similarity [51]. As the incidences of anti-drug antibody formation are rather low in the reference product (incidence of 3%, no drug neutralization capacity detected as described in section 6.2 of the prescribing information of U.S.-licensed Neupogen [2]), it is expected to be also low in the proposed product [37]. The formation of anti-drug antibodies was analyzed in samples taken from the clinical study EP06-302. All samples were finally tested negative for ADA after false positives were confirmed as negative results [44] which confirms the low immunogenic potential of filgrastim and supports the similarity of EP2006 and its reference product.

Two non-clinical studies (EP06-003: local tolerance study; EP06-006: 28-day repeated toxicology study) were submitted for the assessment of pharmacology and toxicology. As observed for the reference product, reversible effects on spleen, liver, and bone marrow have been detected. Minor differences were observed in exposure, but are not expected to have a clinical impact. Therefore, the animal studies support the results of biosimilarity of the products [37].

For demonstration of similarity regarding clinical pharmacology, i.e. pharmacokinetic and pharmacodynamic, four studies conducted with healthy volunteers were submitted, three of which compared EP2006 with the EU-licensed reference product and one with the U.S.-licensed reference product (study EP06-109) [80]. The primary PK endpoints were AUC and C_{max} and for PD ANC and $CD34^{+}$. When comparing the results of EP2006 and the respective reference product of these analyses, similarity was demonstrated as the predefined limits were met. It was concluded that the PK/PD studies provide evidence of the similarity of the proposed product and its reference product as no clinically meaningful differences were observed [80]. In addition, a PK sub-study was conducted as part of study EP06-302 in which the pharmacodynamic profile of EP2006 was

detected to be lower than in the U.S.-licensed reference product [80]. However, this difference was not reflected within the pharmacodynamic analyses because no impact on the clinical outcome was observed although after day 10, the ANC profiles slightly differed [80]. This observation was explained to be caused by the remaining number of patients which was low after day 10 as measurement terminates after recovery of ANC. Overall, these studies contribute to the totality of evidence to demonstrate similarity of EP2006 and the U.S.-licensed reference product. [37, 80]

Two clinical studies analyzing the comparative safety and efficacy of EP2006 with its reference product in patients were submitted for review [74]. Because EP06-302 included the U.S.-licensed reference product, this study was regarded to be of great value for the totality of evidence. Primary efficacy endpoints were the duration of neutropenia (consecutive days ANC<0.5 Gi/L). Secondary endpoints were febrile neutropenia, depths of ANC nadir, and time to ANC recovery. In terms of safety, "incidence, occurrence, and severity of adverse events" [37] as well as immunogenicity were analyzed. The efficacy results demonstrated similarity of the products. Regarding safety, all observed adverse events were concluded to be independent of treatment with either EP2006 or the reference product. No clinically meaningful differences were revealed during the comparative clinical safety and efficacy study. [37, 74]

3.3.3. Discussion

First of all, one has to take into consideration that neither the aBLA pathway was established nor guidance documents were available at the time Sandoz started their development program for Zarxio (refer to Table 3). Therefore, it must have been difficult for Sandoz trying to meet the unknown expectations of the FDA and difficult for the FDA to respond to questions raised during the development process by Sandoz before a consistent approach was set. It can be regarded as if "the FDA is building and living in a house of which the blueprints are not finalized yet" (metaphorical comparison quoted from a colleague).

When looking at the finalized and draft guidelines published by the FDA to date and comparing the requirements listed in these guidelines (refer to section 3.2) to the submitted data (refer to section 3.3.2), one can conclude that the first submitted aBLA meets all requirements the FDA has specified so far, e.g. full CMC data package including the required bridging studies when using a non-U.S.-licensed reference product for analyses, and a clinical study in which the follow-on biologic and the U.S.-licensed reference product are directly compared to each other, to mention just two important requirements. As mentioned before, these guidelines were not published at the time Sandoz started its development program for Zarxio. Therefore, it seems as if the first aBLA was part of setting the standard for the guidelines. One gets the impression as if some of the issues experienced while assessing the aBLA of Zarxio are already reflected in the finalized guidance documents. For example, Sandoz experienced major changes to their manufacturing process during development of EP2006 and provided data was obtained using the "clinical process" product or using the "commercial process" product [37]. The finalized guidance on "Scientific Considerations

in Demonstrating Biosimilarity to a Reference Product" [51] contains a new paragraph addressing this issue, stating that in case of major changes to the manufacturing process during development after completion of the clinical trials, the sponsor has to demonstrate the comparability of the product before and after the change [51]. In case differences are observed, further studies are necessary depending on the extent of observed divergences. So in this case, after the change to the manufacturing process, the protein content was lower and no longer equivalent to the reference product. Therefore, the FDA requested additional data of more batches and finally concluded that the non-equivalence was observed due to the small amount of analyzed batches rather than a result of the changes to the manufacturing process [44].

Furthermore, a statement was inserted in the finalized "general" guidance document [51] stating that "sponsors should justify the selection of the representative lots, including the number of lots." As outlined before, the FDA requested additional data from Sandoz during the assessment [44]. When submitting the additional data, Sandoz clarified that the first set of data submitted was not retrieved from six independent lots but instead of only four independent lots as four of the lots originated from only two bulk batches. Finally, seven independent lots of the "commercial process" product were available for statistical analysis [44]. This example illustrates the importance of thorough justification in terms of choice and number of the batches included in the statistical analysis and explains the reason for the inclusion of the statement in the finalized guideline [51].

It also outlines the importance of statistical analysis regarding positive assessment of an aBLA. However, general guidance for statistical analysis was missing at the time when Sandoz was preparing their submission package and it is still not published to date. As stated in the CMC review [65], the FDA conducted its own statistical analysis of quality data and applied a tiered approach in statistical testing depending on the criticality of the quality attribute. Some assumptions made by Sandoz, e.g. pooling of data from U.S.-licensed and EU-licensed reference product were not accepted and regarded as invalid by the FDA as the similarity has to be demonstrated for the proposed product to the U.S.-licensed reference product [65]. Furthermore, the acceptance criteria established by Sandoz did not take into account the criticality of the attribute and were too wide in certain instances [65]. It is common practice that the FDA statistically evaluates the provided data on its own. However, it is of great importance for sponsors that they understand the approach of the FDA to be able to come to the same conclusions. Otherwise surprises during assessment of the aBLA might occur. If the sponsor cannot evaluate and conclude on equivalence of their proposed product to the reference product on their own, it becomes difficult to submit a promising aBLA. However, sponsors still have to wait for a general guidance because the FDA has just started planning on publishing guidance on "Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity" [94]. So, it will take some time until a draft document will be published.

It can be concluded that the FDA is still in the process of optimizing and defining the requirements necessary for submission of an aBLA. Because the FDA is learning while assessing different

aBLAs and while commenting on the requests addressed by sponsors during BPD meetings, it takes time until respective guidelines are published by the FDA and until sponsors know what to expect during the assessment of their submitted aBLA.

4. Comparison of approval of Zarxio in the U.S. and Zarzio in Europe

Comparing the approval process and the submitted as well as required data for the first biosimilar granted MA in the U.S. reveals differing approaches of the European and U.S. agencies in approving biosimilars.

4.1. European Background Information on the Approval of Zarzio

4.1.1. Regulatory Framework in Europe

In the interests of harmonization in the established European Economic Community, the first pharmaceutical directive was adopted by the European Economic Community in January 1965. Directive 65/65/EEC laid down the legal basis for the MA of proprietary medicinal products as well as for the so-called generics which did not need to be registered at all before the adoption of this directive.

However, the legal framework for granting MA for so-called “biosimilars” was established when Directive 2001/83/EC was amended by Directive 2004/27/EC on March 31st, 2004.

As described in recital 15 of Directive 2004/27/EC, it is necessary to lay down the provisions for biological medicinal products which are similar to a reference product but which do not meet the requirements to be approved as a generic medicinal product. Therefore, Article 10(4) and Section 4, Part II, Annex I of Directive 2001/83/EC were amended accordingly and the legal basis for an abbreviated approval pathway for biosimilars was established in the EU.

In Europe, the first medicinal product to be granted MA as biosimilar was Omnitrope from Sandoz in April 2006. Its application had been submitted on July 1st, 2004 according to the newly established pathway for biosimilars pursuant to article 10(4) of Directive 2001/83/EC as amended [63, 73].

Zarzio from Sandoz - a filgrastim biosimilar - was approved by the European Commission in February 2009 [63] after MAA was submitted to the European Medicine Agency (EMA) on September 6th, 2007 [16].

4.1.2. Guidance for similar biological medicinal products in Europe with regards to Filgrastim

Finalized guidelines for clarification of the requirements for biosimilar MA were first published by the EMA in 2005. Because the biosimilars are rather complex, the requirements for the MAA of these molecules cannot be fully laid down by general guidelines. Therefore, the EMA has published several product class specific guidelines in order to adequately address the requirements for such diverse and heterogenic molecules and to provide the best possible guidance to the applicants.

When looking into the guidelines which represented the basis for requirements of the MAA for Zarzio which was filed with the EMA in 2007, one has to consider the guidelines published in 2005 (refer to Table 4). Since then, the guidelines where updated and the updated versions were published in 2014/15.

Table 4 lists the relevant guidelines for biosimilars in general and the product specific guideline for G-CSF. The reference number and the date of coming into effect are listed for the currently valid guidelines or the currently updated documents, respectively, as well as for the formerly valid guidelines which were effective at the time when the MAA for Zarzio was filed with the EMA.

Table 4 European biosimilar guidelines including the G-CSF product specific guideline in 2005/06 vs. 2014/15

Title of Guideline	**Reference number/** **Effective date**	**Updated Reference number/** **Updated effective date**
Similar biological medicinal products	CHMP/437/04 Effective date: October 30th, 2005	CHMP/437/04 Rev. 1 Effective date: April 30th, 2015
Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues	EMEA/CHMP/BWP/49348/2005 Effective date: June 1st, 2006	EMA/CHMP/BWP/247713/2012 Effective date: December 1st, 2014
Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues	EMEA/CHMP/BMWP/42832/2005 Effective date: June 1st, 2006	EMEA/CHMP/BMWP/42832/2005 Rev. 1 Effective date: July 2015
Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - Guidance on biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor (rG-CSF)	EMEA/CHMP/BMWP/31329/2005 Effective date: June 1st, 2006	
Revision of the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant granulocyte-colony stimulating factor *(Concept paper)*		EMA/CHMP/BMWP/214262/2015 Released for consultation in July 2015 Deadline for comments October 31st, 2015 Draft guideline expected in 2016

Below, the main aspects of each guideline, published at the time when MAA for Zarzio was submitted to EMA, are outlined.

Guideline on Similar biological medicinal products [18]:

This guideline outlines the concept of the "similar biological medicinal products" approach:

- key concept: -"comparability exercise" [18]

- quality data in accordance with Module 3 of the common technical dossier (CTD) required [18]

- all data compliant with European Pharmacopoeia and published guidelines of ICH and Committee for Medicinal Products for Human Use (CHMP) [18]

- reference product: MA granted according to Article 8 of Directive 2001/83/EC [18]

- reference product used during the "comparability exercise" has to be authorized within the EU, studies including a medicinal product authorized in another country can only be submitted as additional data [18]

- same pharmaceutical form, strength and route of administration recommended for the biosimilar and its reference product [18]

- demonstration of similarity for the molecular structure of the active substance of the biosimilar and its reference product [18]

- any observed differences have to be thoroughly justified regarding their impact on safety and efficacy and if indicated, supported by additional data [18]

- agency recommends to seek guidance from the agency in case of any uncertainties or unavailability of product-specific guidance [18].

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues [21]:

This guideline focuses on the quality comparability exercise which has to take into consideration the choice of reference product, the analytical methods including physicochemical properties, biological activity, purity and product- and process-related impurities, and specifications stated in accordance with Q6B [70] as well as the demands for the manufacturing process of "similar biological medicinal products containing recombinant DNA-derived proteins and their derivatives" [21]. The following aspects are described within this guideline:

- introduction of the "stepwise approach" in demonstrating similarity. The extent of differences in quality characteristics will impact the extent of subsequent studies [21].

- comparability exercise cannot be solely performed by referencing data published in Pharmacopoeias or in scientific publications [21]

- in case not all necessary information regarding the reference product is publicly available, own analyses of the reference product including purification and analyses of the active substance of the reference product have to be performed [21]

- state-of-the-art technologies should be used for all analyses [21]

- verification of consistency and robustness of the manufacturing process by the applicant, especially when changes to the manufacturing process occur during product development [21]

- recommendation to use the finished product produced for commercialization for clinical studies [21]

- shelf life of the reference product has to be taken into consideration for all comparative quality analyses [21]

Guideline on Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues [20]:

The guideline outlines the requirements regarding the pharmaco-toxicological tests (non-clinical studies), the pharmacokinetic (PK) and -dynamic (PD) studies as well as the efficacy studies (clinical studies) and the clinical safety studies and risk management plan focusing on the immunogenic potential of the biosimilar [20]. All studies should be performed in a stepwise manner.

Extrapolation to other indications than data was provided for might be feasible if the MoA is identical in each of the indications MA is applied for or if scientific literature and clinical experience is available. Subpopulations have to be addressed separately with regards to safety concerns [20].

The non-clinical studies should comprise *in vitro* (e.g. "receptor-binding studies, cell based assays" [20]) and *in vivo* studies analyzing the PD effect, non-clinical toxicity (at least one repeat dose toxicity study incl. toxic kinetic analyses, i.e. antibody titer, cross reactivity, neutralizing capacity) and specific safety concerns. The species and duration of the study should be applicable to determine the selected endpoints. Any uncertainty regarding safety revealed in the repeat dose study triggers further toxicological studies [20].

For clinical studies, it is emphasized to perform the comparability trial with the biosimilar product ready to be commercialized. If this recommendation is not followed, a sound justification including data has to be provided [20].

Main objectives of PK studies: revealing differences in clearance and elimination half-life and similarity in absorption and bioavailability of the biosimilar and its reference product [20].

Main objectives of PD studies: demonstration of efficacy of the biosimilar in comparison to its reference product; dose selection from the steepest gradient of the dose-response curve recommended [20].

A single combined PK/PD study is acceptable to demonstrate clinical comparability in case PK and PD, including MoA and dose-response curve, are well characterized for the reference product, and a well-known surrogate marker for efficacy should be available for the biosimilar [20].

A pivotal trial to demonstrate comparability of the biosimilar to its reference product is mandatory. The comparability range has to be determined in advance and clinically justified [20].

For clinical safety, data of observed differences in the safety profile has to be provided. Therefore, a risk management and a pharmacovigilance plan in accordance with the European laws and guidelines including the commitment to conduct and monitor post-approval studies have to be submitted [20].

The immunogenic potential of the biosimilar has to be investigated in each indication licensure is sought for. Data on formation of anti-drug-antibodies (ADA) in an appropriate number of patients has to be provided. Long-term results need to be provided, especially in case of chronic administration of the proposed product, i.e. follow up data has to cover at least one year pre-licensure [20].

Annex to Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor (EMEA/CHMP/BMWP/31329/2005) [19]:

This document provides guidance for the applicant regarding the relevant quality, non-clinical and clinical studies for a MAA of a rG-CSF according to Art. 10(4) of Directive 2001/83/EC [19].

Structural differences of a rG-CSF produced in *E.coli* in comparison to the human G-CSF comprise an additional amino-terminal methionine and no glycosylation, one free cysteinyl residue and two disulphide bonds which can be determined by respective physico-chemical and biological methods. The MoA includes a single affinity class of receptors. Formation of anti-drug antibodies is rarely observed for marketed rG-CSF with minor impact on efficacy and safety [19].

In vitro cell based bioassays or receptor-binding assays are recommended as appropriate non-clinical *in vitro* PD-studies. An adequate amount of dilutions should be analyzed for determination of a representative dose-response curve [19].

Non-clinical *in vivo* studies should be based on rodent models, neutropenic and non-neutropenic [19].

A repeat dose toxicity study of a duration of at least 28 days should be conducted in accordance with the “Note for guidance on Repeat Dose Toxicity” (CPMP/SWP/1042/99) [88] including analyses of PD and toxicokinetic in accordance with the "Note for Guidance on Toxicokinetics: A Guidance for assessing systemic exposure in toxicological studies (CPMP/ICH/384/95)” [17].

Data on local tolerance in at least one species should be provided [19] in accordance with the “Note for Guidance for Non-clinical Local Tolerance Testing of Medicinal Products (CPMP/SWP/2145/00)” [89].

For clinical PK studies, “single dose crossover studies using subcutaneous and intravenous administration” [19] determining AUC as primary and C_{max} $T_{1/2}$ as secondary PK marker are recommended. The absolute neutrophil count (ANC) is the primary marker of choice and $CD34^+$ cell count the secondary marker for PD studies. It might be useful to test various dose levels which should be chosen from the steep part of the dose-response curve [19].

The following study design is recommended for the pivotal comparative trial: It is recommended to set up a two-arm comparability trial with patients receiving rG-CSF as prophylaxis of severe neutropenia after cytotoxic chemotherapy (same tumor, disease stage) with known frequency and duration of severe neutropenia. This study design will allow the extrapolation to the other indications of the reference product in case the MoA is identical [19]. In case other designs are in favor of the applicant, scientific guidance should be requested from the agency. “The total follow up on patients should be at least six months. The number of patients should be sufficient for the evaluation of the adverse effect profile, including bone pain and laboratory abnormalities” [19].

The risk management plan should include the monitoring of immunogenicity and the occurrence of rare serious adverse reactions, especially when chronically administered, as well as lack of efficacy, especially in hematopoietic stem cell donors [19].

4.1.3. Timeline for approval of Zarzio in Europe

As described above, the legal basis for biosimilar approval in Europe was established in March 2004 refer to section 4.1.1). The first biosimilar guideline came into effect at the end of October 2005 (refer to Table 4) and the product specific guidance on G-CSF containing biosimilar medicinal products in June 2006 (refer to Table 4). Table 5 lists the key dates during the approval process of Zarzio. Even though Zarzio was not the first biosimilar MA was granted in Europe, the dates demonstrate that the approval process took some time. It took three years and five months from scientific advice to MAA. The procedure itself lasted approximately one year and four and a half months.

Table 5 Timeline of the Approval of Zarzio in Europe

June 24th, 2005	Scientific Advice from CHMP
September 6th, 2007	Submission of application for MA to EMA via the centralized procedure according to Article 3(1) and point 1 of Annex of Regulation (EC) 726/2004. Article 10(4) of Directive 2001/83/EC.
September 26th, 2007	Start of procedure
November 20th, 2008	CHMP positive opinion for granting MA
February 6th, 2009	MA was granted

Dates retrieved from CHMP Assessment report of Zarzio [16].

Although the legal basis was already established when Sandoz sought scientific advice from CHMP regarding their development program of Zarzio, this meeting took place before the first biosimilar was approved in Europe on 12th April 2006 [63]. Therefore, one can assume that the EMA was still in the process of learning how to handle and assess biosimilar MAA. One has to take into consideration that at the time of submission of the MAA for Zarzio, several applications were already submitted to the EMA, so the review process was more experienced by the EMA than by the FDA at the time of MAA submission of Zarzio and Zarxio, respectively.

4.2. Comparison of the sequence of the approval processes of Sandoz' Filgrastim in Europe and the U.S.

Figure 1 visualizes the timelines for both approval processes of Sandoz' filgrastim biosimilars in Europe and the U.S. When looking at the timescale, it becomes obvious that the biosimilar approval process in Europe and the U.S. occurred in a consecutive way rather than in parallel. The establishment of the biosimilar approval pathway took place almost exactly six years apart - March 2004 in Europe versus March 2010 in the U.S. The initial advisory meeting with CHMP took place in June 2005 whereas the advisory meeting with the FDA was held in October 2009 discussing the options for the submission of a "full" BLA according to 351(a) of the PHS Act because the abbreviated pathway was not established back then. Another advisory meeting took place six months after establishment of the abbreviated pathway which was held in October 2010. It is interesting that Sandoz' first attempt in seeking advice from the FDA was made after MA was granted for Zarzio in Europe on Feb 6th, 2009. It looks as if they needed their application to be successfully approved by one leading and world-wide respected regulatory agency such as the EMA, before they took a step forward to get the same product licensed in the U.S. In both regions

Sandoz' encountered the problem of not having guidance documents addressing the requirements for a biosimilar MAA published by the respective agency. Therefore, Sandoz had to rely on the guidance obtained during the scientific advisory meetings with the agencies. However, in both regions the MAA was only submitted after the first guidance documents were published (although not yet finalized in the U.S.). From publication of the first guideline regarding biosimilars in Europe in October 2005, it took Sandoz almost two more years until they finally filed their MAA for Zarzio with the EMA in September 2007. In the U.S., the first draft guidelines were published in April 2012 and again it took Sandoz two more years until the MAA for Zarxio was filed with the FDA in May 2014. In between, in November 2013, a BPD Type 4 meeting was held at the FDA which is meant to discuss the final structure of the aBLA before submission. The final preparation until submission took another six months. Comparing the duration of the pre-submission procedure from first advice from the agency to filing of the application, it took Sandoz two years and roughly two months in Europe and three years and seven months in the U.S. counting from the meeting held after the biosimilar approval pathway was established. However, after submission of the MAA, the procedure assessing the application was rather quick in the U.S. compared to Europe. In the U.S., eight months after filing the aBLA with the FDA, the Oncologic Drugs Advisory Committee (ODAC) Meeting took place giving their unanimous recommendation for approval of Zarxio in all indications applied for. Final MA was granted on March 6th, 2015. In Europe, the positive CHMP opinion was published in November 2008 which means one year and two months after filing the application with the EMA. Therefore, the procedure assessing the MAA took four months longer than in the U.S. The final MA was granted on February 6th, 2009. The duration of two months from the advisory committee meeting in the U.S. or CHMP in Europe, respectively, was comparable in both regions.

In conclusion, the duration of both procedures in the U.S. and Europe, respectively, from the first advisory meeting with the agency until MA was granted was slightly faster in Europe lasting three years and seven months whereas in the U.S. it took four years and five months. However, in Europe as well as in the U.S., it took five years from establishing the abbreviated biosimilar approval pathway until licensure was received. So, one can conclude that both procedures were of comparable duration. The main difference that was revealed is the successive implementation of the procedures. In addition, one has to mention that in Europe several biosimilars had been already approved within the five years from establishing the abbreviated biosimilar approval pathway until licensure of Zarzio [63] in contrast to the five year period in the U.S. without any biosimilar approval.

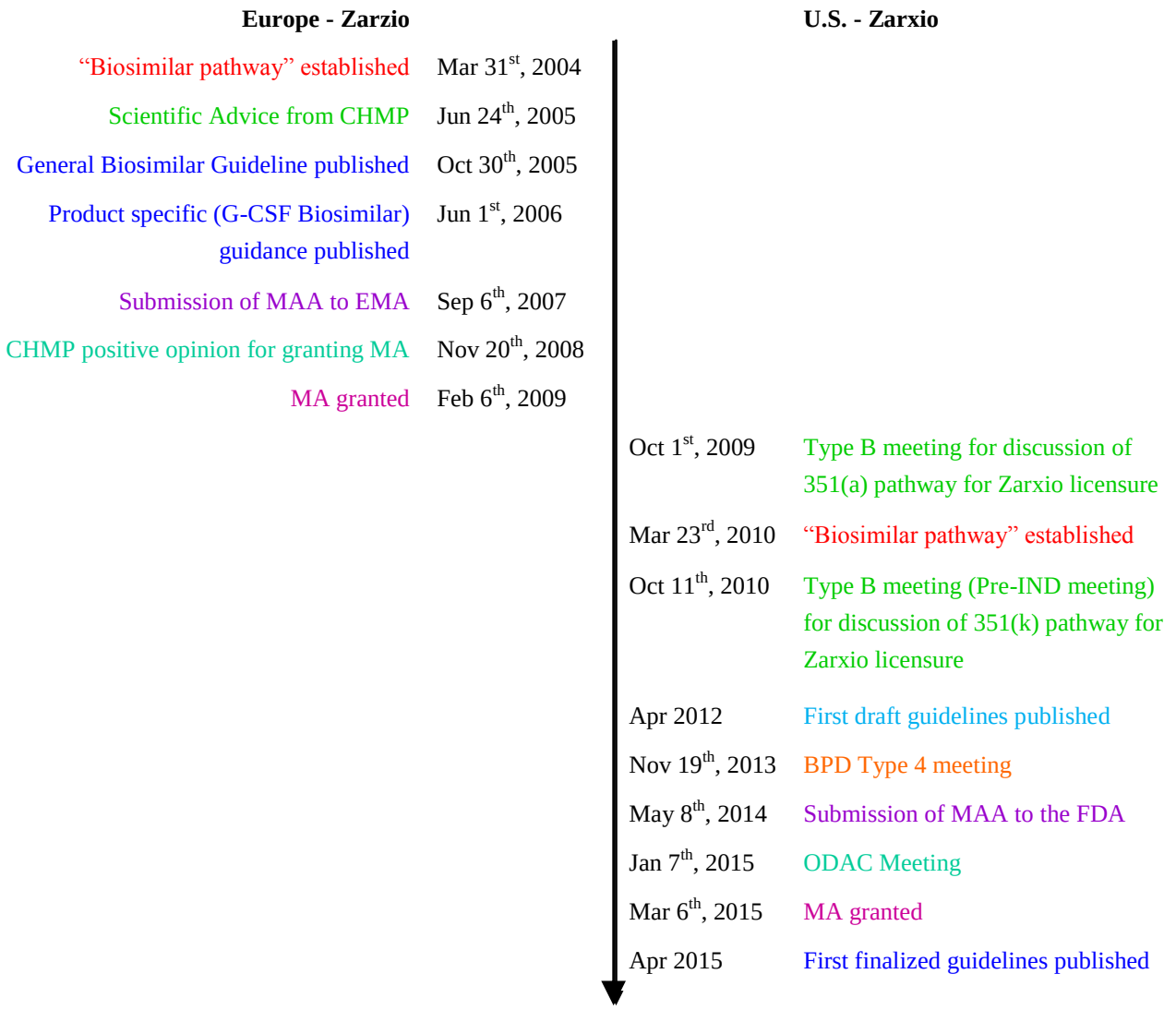

Figure 1 Comparative presentation of the timescales of the biosimilar approval process for Sandoz' filgrastim in Europe (left-hand column) and in the U.S. (right-hand column), same color of text indicates comparable events

4.3. Comparison of studies submitted for approval of Sandoz' Filgrastim in Europe and the U.S.

Comparing the analyses submitted for approval is of interest to reveal differences of the agencies' views on biosimilar approval.

Comparative quality analyses:

In the EU, the characterization of the drug substance of EP2006 (filgrastim) was performed according to recommendations made by the EMA obtained at a scientific advice meeting held on 24th June 2005 because respective finalized guidelines had not even been published. In the U.S., guidelines were also pending when Sandoz started its development program of Zarxio. The required

analyses to demonstrate biosimilarity had to be discussed with the FDA and are most likely based on their recommendations. A comparative presentation of the attributes which were analyzed and submitted as part of the MAA of Zarzio in Europe and the aBLA of Zarxio in the U.S. are listed in Table 6. In addition, this table summarizes the results described in the respective assessment reports.

Table 6 List of Quality Analyses reviewed for MAA of Zarzio in Europe compared to aBLA of Zarxio in the U.S.

	EU: MAA of Zarzio	**U.S.: aBLA of Zarxio**
Quality analyses	Analyses according to CHMP assessment report [16]	Analyses according to CMC Review of Center for Drug Evaluation and Research (CDER) [65]
	- protein structure (primary, secondary, tertiary structure including sequence and folding) - charge characteristics analyzed by isoelectric focusing, cation and anion chromatography - product- (standard and stress tested) and process-related impurities (e.g. aggregates/ truncated forms, deaminated species; oxidized species) - biological characteristics analyzed by bioassay (NFS-60 cell proliferation assay in accordance with Ph.Eur.), western blotting, surface plasmon resonance spectroscopy	- primary protein structure - higher order structure (secondary, tertiary structure) - protein content - clarity - sub-visible particles - product-related substances and impurities (i.e. high molecular weight variants/aggregates; covalent dimers; oxidized species; partially reduced variants; sequence variants; formyl-Met1 species; succinimide species; phosphoglucunoylation; acetylated variants; N-terminal truncated variants; norleucine species; deamidated species) - bioactivity (NFS-60 cell proliferation assay) - receptor binding

	Comparability EP2006 vs. EU-licensedNeupogen - comparability demonstrated regarding protein structure, molecular mass/ size, hydrophobicity, charge, binding and *in vitro* bioactivity - difference regarding buffer (Zarzio: Glutamate, Neupogen: Acetate) due to patent issues - no significant differences for aggregates and truncated forms - deamindated and oxidized forms at lower levels → no impact on bioactivity and stability Composition quantitatively identical, except for buffer system	**Bridging studies: Comparability EP2006 vs. U.S.-licensed Neupogen vs. EU-licensed Neupogen** - if differences were observed, it was always thoroughly discussed and justified that a clinical impact is not anticipated and similarity was concluded for all analyzed parameters, without remaining residual uncertainties

When looking at the extent of quality analyses, one gets the impression that more extensive analyses were performed for the U.S. aBLA. However, the detailed analyzing methods were not stated in the European CHMP assessment report of Zarzio [16] so no proof is available, but it is conceivable that most of the methods were performed for both MAA in the EU and the U.S.. Nonetheless, it has to be taken into consideration that European as well as U.S. guidance documents require to provide data obtained by state-of-the-art techniques. Between 2005 and 2009, when the first meetings with the respective agencies took place to discuss requirements for licensing of EP2006, analytical techniques had most likely been improved and new or improved techniques might have been available for comparability assessment for aBLA of Zarxio in the U.S. compared to the MAA of Zarzio in Europe.

The bridging studies which had to be provided as part of the aBLA in the U.S. because many studies were performed using the European reference product were a major difference between the two submissions. The prerequisites to submit studies performed with a non-U.S.-licensed reference product are the submission of so-called “bridging studies” demonstrating similarity of the follow-on biologic with the non-U.S.-licensed as well as with the U.S.-licensed reference product in a pair

wise comparison as described in the Guidance on "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" [51]. So, all analytical characteristic analyses submitted in the U.S. were part of these bridging studies to transfer the comparative data obtained for EP2006 and EU-licensed Neupogen to U.S.-licensed Neupogen. These bridging studies were not required for the EU MAA of Zarzio as only comparative data with an EU-licensed reference product was acceptable for the EMA according to the Guideline on Similar Biological Medicinal Products [18]. In the updated version of this guideline, the EMA changed their view on this topic and now also allows studies performed with a non-EU-licensed reference product in case bridging studies are provided [24].

Another key issue in demonstrating similarity is the approach of statistical analysis of the data. In the CMC review of Zarxio [65], it is described that the FDA favors a tiered approach in analyzing the analytical comparability, i.e. depending on the criticality of the quality attribute, the standards for statistical analysis are adapted. It does not seem as if statistical analysis was of such huge importance to the EMA when assessing the MAA of Zarzio because statistical analyses and results were not discussed in detail [16]. The CHMP assessment report [16] does not emphasize statistics as much as assessment reports of the FDA do [14, 65, 74, 80, 87]. The approach of the two agencies also differs in terms of statistical analyses. The FDA verifies or includes its own statistical analysis in their review process. In contrast, the EMA relies on the statistical analysis performed and provided by the applicant.

A statistical analysis of the protein content of EP2006 and its EU-licensed reference product was not presented in the CHMP assessment report of Zarzio [16]. However, the protein content was analyzed as differences in PK analyses were observed. The protein content of EP2006 was lower than in Neupogen and it was argued that the observed differences were due to differences in purity. The determined PK data was adjusted to the actual detectable protein content [16]. This approach would not have been accepted by the FDA. Differences in protein content were also observed for the "commercial process" product of EP2006 in comparison to U.S.-licensed Neupogen and had to be clarified by the sponsor (refer to section 3.3.2). According to the revised guideline on quality issues in terms of a similar biological product [22], this approach would no longer be accepted by the EMA because the guideline states that the strength of the biosimilar should be determined and should be comparable to the reference product. This is one example which demonstrates that the EMA and the FDA are adjusting as well as aligning their requirements for biosimilar MAA.

Comparative non-clinical analyses:

When looking at the non-clinical studies submitted as part of the MAA of Zarzio in Europe, it is obvious that all studies are in line with the product-specific guidance on similar medicinal products containing rG-CSF [19] (refer to section 4.1.2)

As laid down in 351(k) of the PHS Act, animal studies including the assessment of toxicity are required for an aBLA unless the FDA waives these studies [81]. Studies were submitted (refer to

Table 7) and especially EP06-006 was regarded as pivotal to the application because analyses were performed with the formulation supposed to be marketed in the U.S. (glutamate buffer) in comparison to the EU-licensed Neupogen. Therefore, animal studies were not waived for this aBLA.

Table 7 provides a comparative presentation of the non-clinical studies submitted as part of the MAA of Zarzio in Europe and as part of the aBLA of Zarxio in the U.S. The results regarding the comparability of EP2006 and its corresponding reference product are listed below the description of each study design.

Table 7 List of Non-Clinical Studies reviewed for MAA of Zarzio in Europe compared to aBLA of Zarxio in the U.S.

	EU: MAA of Zarzio	**U.S.: aBLA of Zarxio**
Non-clinical Studies	Analyses according to CHMP assessment report [16]	Analyses according to Pharmacological Review of CDER [87]
Pharmacodynamic (PD) study	*In vivo* assay in normal vs. neutropenic CD rats (each n= 60), subcutaneously, EU-licensed Neupogen vs. Filgrastim (5 (normal)/ 3 (neutropenic) concentrations, 4 days treatment + 8 days recovery), placebo controlled, buffer: EP2006 glutamate; Study **EP06-004** - determination of *in vivo* efficacy by analyzing hematological parameters focusing on the absolute Neutrophil count (ANC) and areas under the effect curve (AUEC), respectively.	same comparative PD study **EP06-004** submitted
	Comparability EP2006 vs. EU-licensed Neupogen - similar pharmacodynamic response in rats	

Repeat-dose toxicity	*In vivo* assay in Wistar rats (n= 72), subcutaneously, EU-licensed Neupogen vs. Filgrastim (2 vs. 3 concentrations, 28 days treatment + 42 days recovery), placebo controlled, buffer: EP2006 acetic acid; Study **EP06-001** Justification choice of dose: - low dose (20 µg/kg/day) corresponds to highest human dose (24 µg/kg/day in patients with severe chronic neutropenia) - high dose (500 µg/kg/day) approx. 20-fold of highest human dose, 50-fold above the dose for mobilization of autologous PBPC* (10 µg/kg/day) Analyzed parameter: White Blood cells (WBC, esp. neutrophils), mean serum G-CSF levels, immunoglobulin levels, anti-drug antibodies (anti-rhG-CSF antibodies) *PBPC: peripheral blood progenitor cell	In addition to **EP06-001** a second 28-day study was submitted: **EP06-006** (pivotal study) conducted with formulation manufactured for the U.S. market (buffer: EP2006 glutamate): *In vivo* assay in Wistar rats (n= 278), subcutaneously, EU-licensed Neupogen vs. Filgrastim (2 vs. 3 concentrations, 28 days treatment + 42 days recovery), placebo controlled, buffer: EP2006 glutamate Analyzed parameters: Mortality, clinical symptoms, body weight, feed consumption, ophthalmoscope/ auditory examination, neurological tests, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, histopathology, bone marrow, immunogenicity (serum Immunoglobulins, anti-rhG-CSF antibodies, toxicokinetic (C_{max}, AUC))
	Comparability EP2006 vs. EU-licensed Neupogen - comparable results observed, no drug related deaths occurred - immunogenicity comparable in all groups (incl. placebo)	**Comparability EP2006 vs. EU-licensed Neupogen** - comparable results at matched dose levels observed - anti-rhG-CSF antibodies higher in Neupogen than EP2006 treated animals

Toxicokinetics	*In vivo* assay in Wistar rats (n= 50), subcutaneously, EU-licensed Neupogen vs. Filgrastim (3 concentrations, 14 days treatment), placebo controlled, buffer: EP2006 acetic acid; Study **EP06-002** - determination of serum concentration C_{max} (kinetics/ bioavailability) and Area under the curve (AUC 0-14d), mortality, body weight	Analyses of toxicokinetic are conducted in study **EP06-002** and in study **EP06-001,** and **EP06-006 (**refer to 'Repeat-dose toxicity')
	Comparability EP2006 vs. EU-licensed Neupogen - comparable results at matched dose levels observed	
Local tolerance	Study **EP06-003**	Study **EP06-003**
	In vivo assay in New Zealand White Rabbit (n= 36), subcutaneously, para-venously, intra-venously, intra-muscularly, intra-arterially, EU-licensed Neupogen vs. EP2006 (acetic acid buffer) vs. EP2006 (glutamate buffer) (single dose), placebo controlled (contralateral); Study **EP06-003** Endpoints: erythema, edema, hematomas, pain reactions, gross pathology, histopathology	
	Comparability EP2006 vs. EU-licensed Neupogen - identical local tolerance, no differences detected	
	Additional study: Determination of rhG-CSF in rat serum using ELISA (not in accordance with GCP)	

- Secondary pharmacodynamics - Safety pharmacology - Pharmacodynamic drug interaction - Pharmacokinetics - Single dose toxicity	- not performed in accordance with "Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor" [19] as further toxicity studies are not listed as required documentation	- not submitted/ not applicable as stated in the pharmacological review [87]
Genotoxicity Carcinogenicity Reproduction Toxicity	- not performed in accordance with "Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor" [19] as further toxicity studies are not listed as required documentation	- not applicable as stated in the pharmacological review [87]

When comparing the studies submitted for review in Europe and in the U.S., it shows that besides study EP06-006, all non-clinical studies submitted for review by either the EMA or the FDA were identical. No residual uncertainties remained and therefore, no additional non-clinical studies were triggered, neither in Europe nor in the U.S..

Interestingly, when comparing the requirements described in the initial European guideline [20] compared to the revised guideline [25], a clear shift regarding the importance of non-clinical studies can be observed. Directive 2010/63/EU "on the protection of animals used for scientific purposes" [90] strengthens the animal welfare and according to this directive, the necessity of every single non-clinical study has to be carefully reconsidered. In addition, the value of *in vitro* analyses of pharmaco-toxicology is regarded to be potentially more specific and sensitive and the differences observed can be of higher significance than comparable *in vivo* studies. Therefore, dismissal of non-clinical *in vivo* studies is possible in case conclusive data of *in vitro* studies is available.

This approach is described in a similar manner in the finalized general U.S. guidance on biosimilars [51]. In the U.S., *in vitro* studies should be considered in case "animal toxicity studies are not warranted based on an acceptable scientific justification". However, it is stated that the *in vitro* tests can be of value if no suitable animal model is available [51].

Comparative clinical studies

Table 8 lists all clinical studies which were reviewed by the respective agencies for either MAA of Zarzio in Europe or for aBLA of Zarxio in the U.S. The summarized outcome of the comparability assessment of EP2006 with the respective reference product is listed either at the end of each subsection of Table 8 or after the outlined study design of a specific study.

Table 8 List of Clinical Studies reviewed for MAA of Zarzio in Europe compared to aBLA of Zarxio in the U.S.

	EU: MAA of Zarzio	**U.S.: aBLA of Zarxio**
Clinical studies	Data retrieved from CHMP assessment report [16]	Data retrieved from CDER assessment reports of Zarxio: Clinical Review [74], Clinical Pharmacology and Biopharmaceutics Review(s) [80], Pharmacology Reviews [87], and Cross Discipline Team Leader Review [13]
Clinical Pharmacology		
PK/PD Phase I *(healthy volunteers)*	**EP06-101:** study design: randomized, double blind, 2-way crossover, 40 healthy volunteers, multiple s.c. doses EP2006 (filgrastim) vs. EU-licensed Neupogen, 10 µg/kg/day; primary objective: PK† bioequivalence secondary objective: PD*, safety	In addition to **- EP06-101** **- EP06-102** **- EP06-103** **- EP06-105** (supportive data for bridging analyses) two more studies were submitted: **- EP06-109** **- EP06-104**
	EP06-102: study design: randomized, double blind, 2-way crossover, 26 healthy volunteers, single i.v. dose EP2006 (filgrastim) vs. EU-licensed Neupogen, 5 µg/kg/day; primary objective: PK† bioequivalence secondary objective: PD*, safety	**EP06-109:** study design: randomized, double blind, 2-way crossover, 26 healthy volunteers; single s.c. dose EP2006 (filgrastim) vs. U.S.-licensed Neupogen, 10 µg/kg/day; primary objective: PD (ANC_{max}, $AUEC_{0\text{-}120h}$); PK ($AUC_{0\text{-}last}$, C_{max}), secondary objective: $CD34^+$, safety

	EP06-103: study design: randomized, double blind, 2-way crossover, two dose groups, 2 × 28 healthy volunteers, multiple s.c. doses EP2006 (filgrastim) vs. EU-approved Neupogen, 2.5 µg/kg/day and 5 µg/kg/day (chosen from steep part of dose-response curve); primary objective: PD* equivalence secondary objective: PK†, safety	**Comparability EP2006 vs. U.S.-licensed Neupogen** - comparable results observed - supportive data for bridging analyses
	EP06-105: study design: randomized, double blind, 2-way crossover, 24 healthy volunteers, single s.c. dose EP2006 (filgrastim) vs. EU-licensed Neupogen, 1 µg/kg/day; primary objective: PD* equivalence secondary objective: PK†, safety	**EP06-104:** study design: randomized, double blind, 3-way crossover, 28 healthy volunteers; single s.c. dose EP2006 (filgrastim, Glutamate and Acetate formulation) vs. EU-licensed Neupogen (Acetate), 2.5 µg/kg/day; primary objective: PK ($AUC_{0\text{-last}}$, C_{max}) secondary objective: ANC_{max}, $AUEC_{0\text{-last}}$); safety
	*__PD endpoints:__ AUEC of absolute neutrophil count (ANC) and of absolute $CD34^+$ count, predefined equivalence intervals: 2.5 µg/kg/day: 87.25% - 114.61%; 5/10 µg/kg/day: 86.50% - 115.61% **Comparability EP2006 vs. EU-licensed Neupogen** - AUEC of ANC within the equivalence interval	**Comparability EP2006 (acetate) vs. EU-licensed Neupogen** - equivalent results **Comparability EP2006 (glutamate) vs. EU-licensed Neupogen** - lower C_{max} and $AUC_{0\text{-last}}$ observed for EP2006 (glutamate) than for the reference product → no differences in ANC as well as safety signals observed, i.e. no impact on PD [80, 87]

	†**PK endpoints:** AUC_{0-24h} and C_{max}, acceptance range 80 - 125% (according to "Guideline on the Investigation of Bioequivalence" [11]) **Comparability EP2006 vs. EU-licensed Neupogen** - bioequivalence for C_{max} not completely demonstrated although protein content correction was applied → no meaningful impact on PD anticipated	
Clinical efficacy		
Phase III clinical studies: *(patients)*	**EP06-301**: study design: open, single-arm, multicentre study, chemotherapy-naive breast cancer patients (n=170), treatment with doxorubicin and docetaxel, filgrastim as prophylaxis for severe neutropenia; treatment scheme: 30 MIU body weight < 60 kg, 48 MIU ≥ 48 MIU from day 2 of chemotherapy cycle for up to 14 days or until ANC 10×10^9/L post nadir, duration: 3 months ≈ 4 treatment cycles active treatment, 3 months follow-up Efficacy endpoints: - incidence and duration of severe neutropenia in cycles 1 to 4 - incidence of febrile neutropenia - time to neutrophil recovery	In addition to **EP06-301** another efficacy study was submitted: **EP06-302 (PIONEER):** study design: randomized, double-blind, parallel-group, multi-center study, 4 groups [EP2006 and US licensed Neupogen each alone (groups 1 and 4) and alternated starting with one of the two (groups 2 and 3)], breast cancer patients (n=214) receiving TAC chemotherapy (docetaxel, doxorubicin, cyclophosphamide on day 1), six treatment cycles à 21-days; treatment scheme: 5 µg/kg from day 2 of chemotherapy cycle for up to 14 days or until ANC 10×10^9/L post nadir, primary study objective: non-inferiority regarding mean duration of severe neutropenia (number of consecutive days ANC < 0.5×10^9/L) in cycle 1; (post hoc 2-sided analysis performed by the FDA [74])

	Comparability EP2006 vs. EU-licensed Neupogen Comparison was made to published data for Neupogen → no direct comparison of filgrastim and reference product; therefore of limited value for comparability exercise, reviewed as supportive data According to the scientific advice: - PD study in healthy volunteers sufficient to demonstrate comparability of the efficacy - extrapolation to all indications of the reference product acceptable because of identical MoA	key secondary study objectives: febrile neutropenia, days of fever, ANC nadir, time to ANC recovery [74] sub-study objective: PK (AUC, C_{max}) **Comparability EP2006 vs. US licensed Neupogen** - equivalent efficacy - no meaningful clinical differences Sub-study: AUC and C_{max} lower in EP2006 than in Neupogen → no clinically meaningful impact on PD observed
Clinical safety		
Healthy volunteers	**EP06-101 - EP06-103; EP06-105:** - comparison of safety profile (Adverse drug reactions - ADR) in healthy volunteers treated with filgrastim or EU licenesed Neupogen **Comparability EP2006 vs. EU-licensed Neupogen** - comparable occurrence of ADRs in healthy volunteers	**EP06-101 - EP06-103; EP06-105, EP06-109:** - due to successful bridging analysis these studies conducted with EU-licensed Neupogen were considered as supportive data regarding safety assessment [74]
Patient exposure	**EP06-301**:(refer to Clinical efficacy): primary objective: safety and immunogenicity - analyzing occurrence of	**EP06-302:** (refer to Clinical efficacy) n=190, all six treatment cycles + 4 weeks follow-up after last administration; primary objective: safety (main study assessing safety) and

	treatment emergent adverse events (G-CSF- and non-G-CSF-associated) in patients - no adverse event was observed in terms of local tolerance	immunogenicity - analyzing treatment related deaths, adverse events, incl. serious adverse events (SAE), adverse events of interest, common adverse events, immunogenicity, standard laboratory analysis **Comparability EP2006 vs. U.S.-licensed Neupogen** - comparable occurrence of ADRs in patients
Immunogenicity	- immunogenicity analyzed by measuring anti-rhG-CSF antibodies in samples from **EP06-101, EP06-102, EP06-103** **Comparability EP2006 vs. EU-licensed Neupogen** - no anti-rhG-CSF binding antibodies were detected in any of the analyzed samples.	- immunogenicity analyzed by measuring anti-rhG-CSF antibodies in samples from **EP06-109 (healthy volunteers), EP06-302 (breast cancer patients)** **Comparability EP2006 vs. U.S.-licensed Neupogen** - after confirmatory assay no anti-rhG-CSF binding antibodies were detected in any of the analyzed samples
Post marketing experience	Not applicable	Since June 2009 through January 2014 approximately 6.2 million patient exposure days counted. - no other safety related incidences than reported for the innovator - a few incidences of hypersensitivity reactions were reported, number too small to be detected in clinical trials, an actual (low) risk exists for the incidence of this adverse event [74]

*PBPC: peripheral blood progenitor cell

General aspects for comparison of clinical studies for MAA of Zarzio in Europe and Zarxio in the U.S.

As expected, the application of Zarxio in the U.S. includes additional studies compared to the European MAA of Zarzio. These additional studies EP06-109 and EP06-302 were needed to comply with the Guidance on "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" [51] for direct comparison of EP2006 to the U.S.-licensed reference product Neupogen. Another additional study was assessed by the FDA during their review process. Study EP06-104 compared the different formulations (acetate and glutamate buffer) of EP2006 to the EU-licensed Neupogen. All studies reviewed for MAA of Zarzio were at least regarded as supportive data for assessment of aBLA of Zarxio because the bridging studies outlined in Table 6 demonstrated high similarity of EP2006 to EU-licensed Neupogen as well as to U.S.-licensed Neupogen, so that the results obtained through studies conducted with the European reference product can be regarded as valid data for the aBLA submitted in the U.S.. In addition to the clinical studies listed in Table 8, four more studies were submitted (EP06-106 - EP06-108, and EP06-110) by the applicant as part of the application package of Zarxio. However, as the comparator was a Japanese licensed filgrastim ("Gran") which is not of interest for the assessment of this MAA, these trials were disregarded for review by the FDA [74]. Study EP06-501 was also submitted as supportive data for safety assessment (prospective, observational study of healthy volunteers undergoing peripheral blood progenitor cell (PBPC) mobilization). However, as no comparator was included in this study, it was also disregarded for review by the FDA [74].

Clinical Pharmacology

The clinical pharmacology part is pivotal to the MAA. It is of major importance for demonstrating similarity that the PK- and PD-profile of the proposed product and its reference product are highly similar. The importance to both agencies becomes obvious when looking at the published guidelines. In the U.S., a draft guideline entitled "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product" published in May 2014 addresses this topic explicitly [50]. In the "Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues" [20] published in Europe, it is also stressed that pharmacological PK- and PD-studies are essential for the overall assessment of biosimilarity.

The studies submitted as part of the European MAA for Zarzio revealed slight differences with regards to PK explained by "differences in the levels of purity of the two products, leading to a systematic bias" [16], and although protein content correction was applied, bioequivalence for C_{max} could not be completely demonstrated. However, CHMP concluded that no meaningful impact on PD is anticipated and therefore, biosimilarity was concluded [16]. Although the European guidelines have been updated recently, the approach of "protein correction" is still mentioned and

can be excepted on a case-by-case basis [25]. In the U.S. guidelines the protein content is not explicitly addressed. However, it is stressed to analyze the lot-to-lot variability and to justify the choice of lots used for analyses [51].

Looking at the studies submitted as part of the U.S. MAA for Zarxio, it is obvious that further studies were necessary for assessment of the application. Study EP2006-109 analyzed EP2006 (filgrastim) in comparison to the U.S.-licensed reference product which resulted in comparable results for both medicinal products. This data was regarded as supportive data for the bridging analysis because it has been already demonstrated from a quality point of view that EP2006 is highly similar to the U.S.-licensed and to the EU-licensed reference products. If the clinical pharmacology is comparable between EP2006 and its EU-licensed reference product and EP2006 is comparable to its U.S.-licensed reference product as demonstrated with study EP2006-109, all conducted studies can be regarded to reveal reliable data for the comparative assessment. In study EP2006-104 which analyzed the impact of the formulation buffer, a lower C_{max} and $AUC_{0\text{-}last}$ was observed for EP2006 formulated with glutamate than for the reference product. However, it was argued that no differences in ANC as well as safety signals were observed, i.e. no impact on PD was revealed. The results obtained with the acetate formulation were comparable between both medicinal products. It was concluded that the applied volume is comparatively small and will unlikely impact the efficacy, because the small applied volume will be immediately diluted within the body, so that the efficacy of the medicinal product will be impacted by the physiological conditions in the body. If no differences in PD are observed, the difference in buffer can be neglected [80, 87].

Both agencies followed their guidance documents and allowed extrapolation of the data to all indications MA was applied for, because of the same MoA in all indications [14, 16].

Clinical Efficacy

As mentioned in the CHMP assessment report of Zarzio, Sandoz sought scientific advice regarding the extent of clinical trials necessary for MAA of filgrastim [16]. It was accepted by the EMA that a PD study demonstrating comparability is sufficient for demonstrating comparable efficacy. Therefore, the clinical study including patients (EP06-301) was only submitted as supportive data to the MAA [16]. This study was only single-armed and therefore cannot be regarded as properly controlled. Data was only compared to literature data from studies using Neupogen. When looking into the product-specific guidance on similar medicinal products containing rG-CSF, it is explicitly recommended to provide data of a two-arm comparative clinical trial with patients receiving chemotherapy and in addition, to prevent neutropenia, rG-CSF [19]. Therefore, it is interesting that the EMA accepted Sandoz' approach and waived the necessity of a clinical study in patients. One has to consider that the guidance documents including the product class specific guideline had not been published yet when Sandoz sought scientific advice discussing the development program of

Zarzio. The EMA might have learned from this particular case and might have adjusted the guidance in recommending a clinical trial in patients for products containing rG-CSF [19]. In addition, it is stated throughout their guidance documents that different approaches can always be proposed to and discussed with the EMA [19] which might have taken place during the scientific advice requested by Sandoz and held by CHMP. Nonetheless, approximately 10 years after publishing the product class specific guideline, a concept paper outlines the main aspects for revision of this guidance document, listing the requirements which need to be fulfilled to waive a pivotal clinical trial including safety/ immunogenicity for discussion [23]. Therefore, the updated guidance on similar medicinal products containing rG-CSF most likely will address the requirements for omitting these trials. This demonstrates that the EMA learns and adapts their guidelines according to the experiences they gained during previous years.

In the U.S., an application submitted under section 351(k) of the PHS Act requires clinical data assessing immunogenicity, PK and PD to demonstrate "safety, purity, and potency". The extent of clinical studies results from the residual uncertainties from quality and non-clinical analyses and should be discussed with the FDA. As study EP06-302 was submitted as part of the aBLA, it is most likely that this efficacy study was requested by the FDA which can be regarded as the core study of this application, demonstrating comparable safety and efficacy of EP2006 to the U.S.-licensed reference product. However, a few aspects led to discussions during the review process. Study EP06-302 was originally designed as a non-inferiority study [37]. It is stated in the guideline that an equivalence approach should be favored and a non-inferiority design might only be acceptable in certain circumstances which have to be justified by the sponsor [51]. However, in this case the FDA's opinion differs and the non-inferiority design was not accepted. Therefore, the FDA performed a post hoc 2-sided analysis to ensure equivalence of EP2006 and U.S.-licensed Neupogen [14]. Another aspect that triggered some discussion was the PK sub-study of EP06-302 which revealed lower AUC and C_{max} with EP2006 than with U.S.-licensed Neupogen [80]. The same effect was discussed within the CHMP assessment report of Zarzio in which a PK study revealed lower AUC and C_{max} with EP2006 than with EU-licensed Neupogen [16]. However, in Europe it was accepted to adapt the results according to the actual measurable protein content which resulted in bioequivalence only for AUC and not for C_{max} [16].

Finally, both assessment reports concluded that no effect on PD was observed and therefore, no impact on clinical outcome is expected [13, 16]. This is one example that differences can be observed between the proposed biosimilar and its reference product but it has to be thoroughly justified that an impact on the clinical outcome is not expected, so that high similarity can be concluded nevertheless.

Clinical Safety

The immunogenic potential and the incidence of adverse events are other important aspects of the overall biosimilarity assessment as they have a major impact on efficacy and safety. Therefore it is of importance to gain as much information about these aspects as possible from all studies conducted. It has been stated that respective analyses had been performed for all submitted clinical studies [14]. The low known immunogenic potential of the reference product could be confirmed by the studies conducted. In the U.S., the FDA stressed the importance of analyzing samples of patients which received multiple doses of EP2006. Therefore, samples obtained from study EP06-302 were of major importance and had to be reanalyzed due to technical concerns from the FDA. However, none of the analyzed samples were tested positive for neutralizing anti-drug antibodies [44].

4.4. General Discussion

When comparing both MAA for Zarzio in Europe and Zarxio in the U.S., it has to be taken into consideration that Zarzio was approved in Europe in 2009 whereas Zarxio was licensed in the U.S. six years later in 2015. The development program of both products started many years before the final approval of MA. Both development programs had to be designed on the basis of guidance obtained during an advisory meeting held with the agency because guidance documents were not published yet.

When looking at the content of the guidance documents finalized in 2006 in Europe compared to 2015, it seems as if the U.S. and Europe are aligning their views on biosimilar approval which might be a result of the ‘biosimilar cluster’ which was set up by the FDA and the EMA in 2011 - before the first draft guidelines in the U.S. were published - to collaborate and discuss topics regarding regulations of biosimilars [15] and of the experiences gained from the already licensed and marketed biosimilars in Europe. There have not been many differences between the draft documents published in the U.S. in 2012 and the guidelines published in Europe in 2006 as compared in the Master thesis of E. Baldyga in 2012 [5]. However, some views have been changed since then and besides the finalization of the draft guidance documents published in the U.S. in 2012, the European guidelines have been revised as well and updated versions were published in 2015.

When comparing the assessment process of and required data for the first biosimilar licensed in the U.S. with the respective procedure in Europe, it becomes clear that both agencies basically follow the same ideas. It seems as if the FDA was more thorough in assessing the provided data and as if the sponsor submitted a more extensive data package to the FDA than to the EMA, but this can be explained by the required bridging studies and the most likely improved test methods. However, this was the first biosimilar approval in the U.S. and the assessed molecule was one of the simpler products with regards to structure and molecular size. One has to wait and see how the FDA will

decide on the next biosimilar MAA if their assessment, e.g. regarding extrapolation, differs from the European perspective on this issue.

5. Further biosimilar approvals in the near future?

Finally, the first biosimilar was granted MA in the U.S. in March 2015 [8]. Since then, another year passed by and no further biosimilar has received FDA licensure so far. That raises the question if further biosimilar licensures can be expected in the near future.

Figure 2 shows the continuous increase in BPD programs since January 2013 when the data collection of BPD programs started. Until September 2015 (end of Fiscal Year 2015), 57 BPD programs were registered with the FDA indicating that several potential biosimilar MAA are already in preparation. In Jane Woodcocks testimony regarding 'Biosimilars Implementation' before the Committee on Energy and Commerce - Subcommittee on Health on Feb. 4th, 2016 she stated that until January 21st, 2016, 59 BPD programs referring to 18 different reference products were registered [95] which clearly shows a continuous increase in BPD programs.

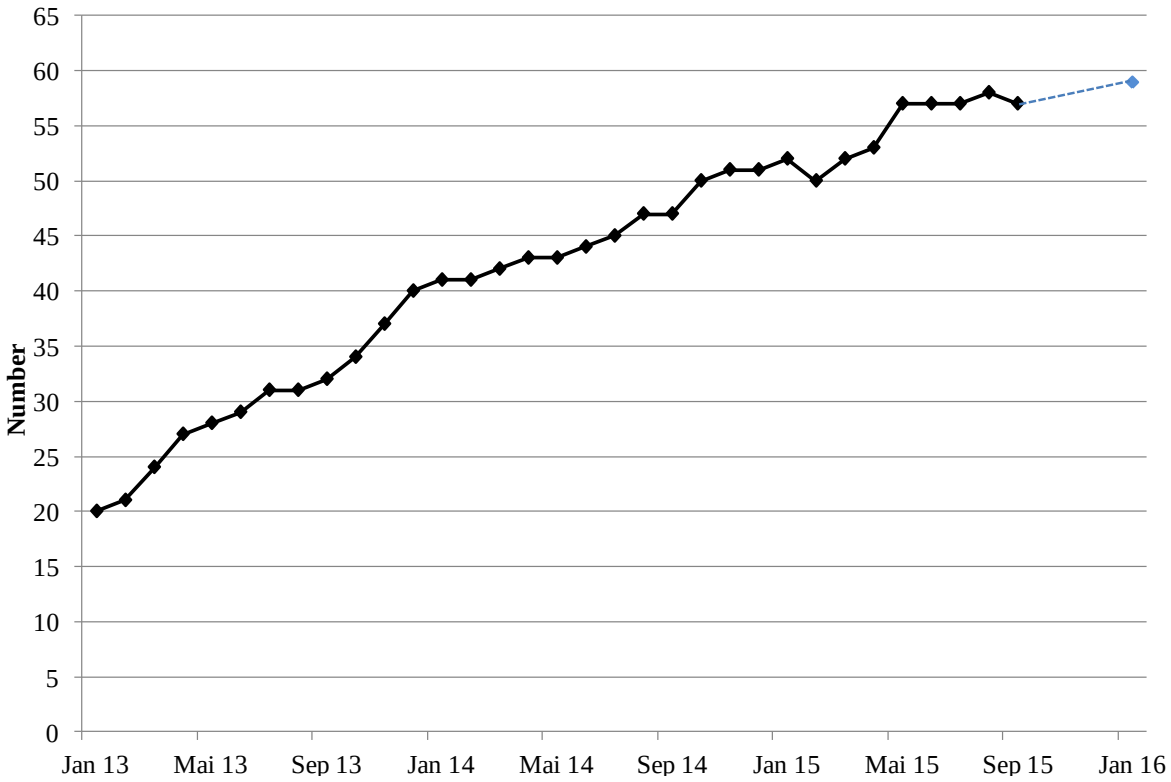

Figure 2 Cumulative number of biosimilar development programs in the BPD program from January 2013 through January 2016 (Data retrieved from FDA website - FDA-TRACK: Agency-wide Program Performance [45] and Jane Woodcocks Testimony before the Committee on Energy and Commerce - Subcommittee on Health on Feb. 4th, 2016 [95]). The dotted blue line indicates that there is no monthly data available between September 2015 and January 2016.

Figure 3 shows that since January 2013, when the FDA started collecting data, until September 2015, 22 investigational new drug applications (INDs) were submitted to the FDA. The submission

of a biosimilar IND triggers the participation in the BPD program (refer to section 3.1) and therefore, the 22 biosimilar INDs are also contained within the data represented in Figure 2. It demonstrates that several clinical studies are ongoing since 2013, generating required clinical data for an aBLA and it is most likely that already prior to data collection for the BPD program, clinical studies required for an aBLA were conducted because the number of BPD programs in January 2013 already started with 20 and it is expected that some of these BPD programs have already started their clinical trials.

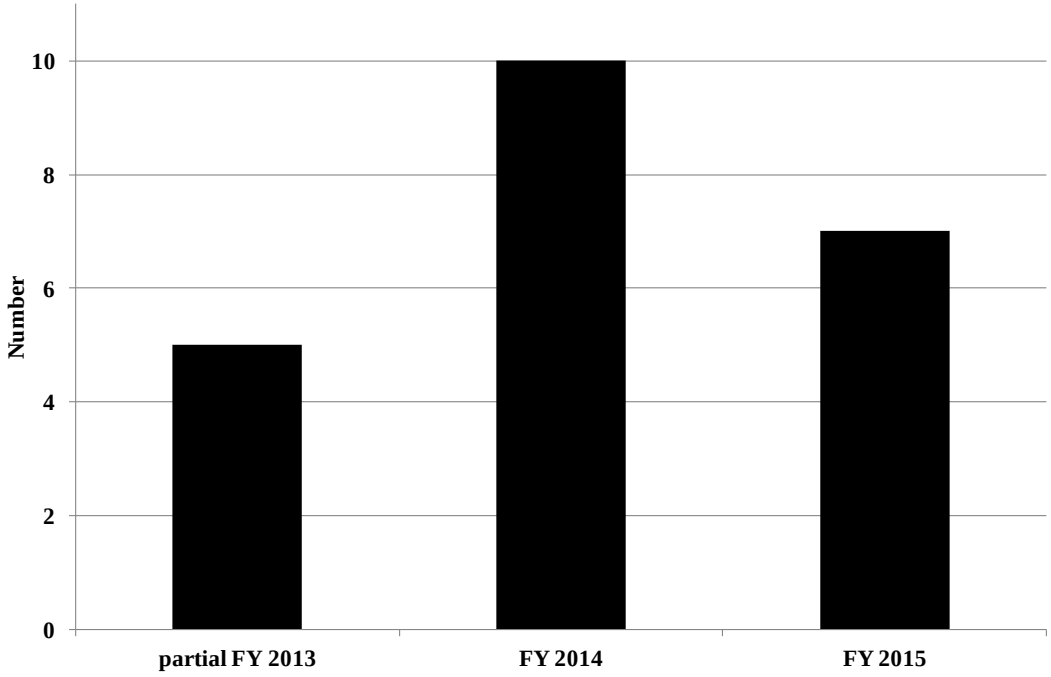

Figure 3 Number of biosimilar investigational new drug applications (INDs) received at the FDA during the partial Fiscal Year (FY) 2013 (Jan to Sep 2013) to FY 2015 (Data retrieved from the FDA website - FDA-TRACK: Agency-wide Program Performance [47])

Figure 4 illustrates the number of scheduled meetings arranged by meeting type including the initial advisory meeting as well as the BPD meeting types 1 to 4. Looking at the columns presented in Figure 4, several aspects become obvious. Firstly, there has been an increase in scheduled meetings, especially from FY2013 to FY2014. There has been a major increase in all possible meeting types during FY2014 compared to FY2013. For example, 9 initial advisory meetings were scheduled which represent approximately 2/3 of all initial advisory meetings since the beginning of data collection. As it takes a while from setting up a BPD program until submission of an aBLA, it will take another few years until MAA for these potential biosimilars will be filed with the FDA. However, it demonstrates that many development programs are ongoing preparing MAA for biosimilars under 351(k) of the PHS Act in the U.S. and are progressing towards submission. Secondly, the pattern of distribution of the different meeting types has clearly changed, especially from FY2014 to FY2015, demonstrating the importance of meeting type 2, increasing requests for

meeting type 1, and lower interest in meeting type 3 by the sponsors (for explanation of meeting types refer to section 3.2). Mainly meeting type 2 is requested by sponsors seeking guidance on specific issues of their development program combined with a reduction in requests for meetings of type 3 which implies that sponsors favor advice from the FDA on the basis of a review of summary data rather than a review of full study reports which might be caused by the longer scheduling time of 120 days for type 3 meetings compared to 75 days for type 2 meetings [33].

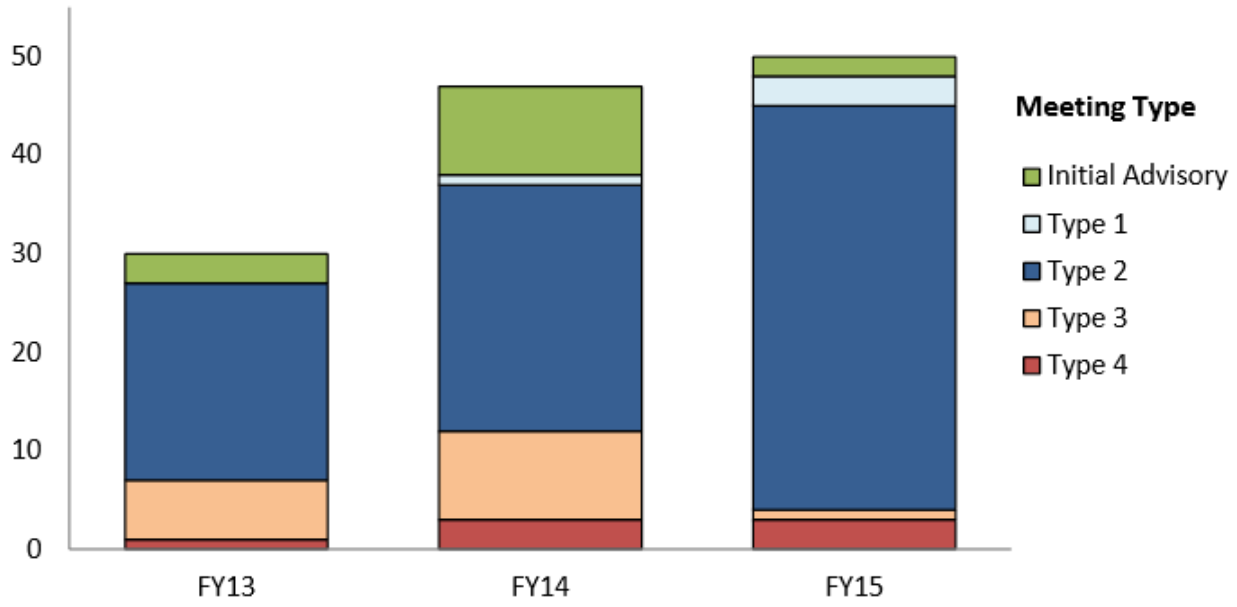

Figure 4 Number of scheduled meetings at the FDA arranged by type from Fiscal Year 2013 to 2015 (figure retrieved from Jane Woodcocks testimony regarding 'Biosimilars Implementation' before the Committee on Energy and Commerce - Subcommittee on Health on Feb. 4th, 2016 [95])

Type 4 meetings will only be granted once and are meant to be held close to submission of the aBLA to discuss the final structure of the application. Therefore, this type of meeting will occur at rare occasions, but with many ongoing BPD programs, it is most likely that this type of meeting will be requested more often in the near future. During FY2014 and FY2015, more type 4 meetings were already scheduled compared to FY2013. Resulting from the number of scheduled type 4 meetings, the question arises whether any other aBLAs have already been submitted to the FDA up to now. There have been 8 submissions of applications for biosimilars according to 351(k) so far (refer to Table 9) which can be directly linked to the 7 scheduled type 4 meetings during FY2013 to FY2015. The 8th type 4 meeting might already have taken place in FY2016.

The estimated goal of a review and approval time of 10 months [33] has only been met for one application to date. This application seeking licensure for Sandoz' filgrastim which is one of the simpler proteins with regards to its molecular structure is the only one which was approved so far (refer to section 3.3). However, some of the other MAA are thought to be close to licensure.

For example, Celltrion expected to receive a positive recommendation for approval of their monoclonal antibody infliximab (CT-P13) from the Arthritis Advisory Committee (AAC) in March 2015. However, in February - three weeks before the scheduled meeting - a note was posted on the official website of the FDA that the meeting had to be postponed until further notice due to pending information requested from the applicant [28]. On January 15th, 2016 the FDA announced the previously postponed meeting to be held on February 9th, 2016 [30]. Celltrion was always in close contact with the FDA and performed additional clinical trials to meet the requirements of the FDA. The data presented at the AAC meeting was regarded as extensive, in particular data supporting the request for extrapolation and also analytical data to demonstrate similarity of the proposed biosimilar and its reference product as well as the bridging data [31]. Finally, the AAC's vote regarding the approval of CT-P13 in all conditions of use which licensure is sought for was 21 for yes vs. 3 for no [31]. Although several uncertainties were discussed, the final vote demonstrates the intention of the U.S. to proceed with this abbreviated pathway and finally its intention to provide access to biosimilars. This is not a binding vote for the FDA. However, it represents the public and independent expert opinion on biosimilars and especially on this aBLA and in the past the FDA followed its advice. Therefore, one can expect the approval of CT-P13 within the next few months of 2016.

Furthermore, Hospira, now a Pfizer company, hoped to receive licensure for its biosimilar Epoetin alfa by the end of 2015 - already exceeding the targeted 10 months approval time frame from the FDA because the aBLA was accepted for review by the FDA in Feb. 2015 [58]. However, as published in October 2015, Hospira received a complete response letter from the FDA regarding their aBLA for Epoetin alfa which means that the FDA is of the opinion that it cannot grant MA for this biosimilar on the basis of the provided data. Hospira is planning resubmission of the application within the first six months of 2016 [91]. By receiving a complete response letter, Hospira is eligible to a type 1 BPD meeting to receive advice on the outstanding issues leading to the complete response letter and hopefully resolving the issues to finally succeed with its resubmission. The set review time goal for a resubmitted application is six months [33], i.e. if this application is resubmitted within the first six months of 2016, MA might be granted within 2016.

In addition, several other applications have already been submitted and are awaiting their approval by the FDA. It seems as if the biosimilar pathway is slowly picking up speed. Looking at the currently expected patent expiration dates for the innovator's products of the follow-on products which an aBLA has already been submitted for (refer to Table 10), it can be expected that finally within the next few years, some biosimilars will be marketed in the U.S. if no extensive patent litigations take place (refer to section 6.3.1).

Table 9 List of submitted aBLA to the FDA

#	**Date aBLA was submitted*/ accepted§ for review by FDA**	**Active substance**	**Company**	**Reference product**	**Lit.-ref.**
1	*Jul 24th, 2014**	*Filgrastim*	*Sandoz*	*Amgen's Neupogen*	*[55]*
2	Aug 8th, 2014*	Infliximab	Celltrion	Janssen Biotech's Remicade	[56]
3	Dec 17th, 2014§	Pegfilgrastim	Apotex	Amgen's Neulasta	[57]
4	Feb 2015§ (Dec 16th, 2014*)	Epoetin alfa	Hospira	Amgen's Epogen	[58]
5	Feb 13th, 2015§	Filgrastim	Apotex	Amgen's Neupogen	[59]
6	Oct 2nd, 2015§	Etanercept (GP2015)	Sandoz	Amgen/Pfizer's Enbrel	[60]
7	Nov 18th, 2015§	Pegfilgrastim	Sandoz	Amgen's Neulasta	[62]
8	Nov 25th, 2015* (Jan 25th, 2016§)	Adalimumab (ABP501)	Amgen	AbbVie's Humira	[3, 61, 73]

*submitted/ §accepted for review by FDA; italic font: aBLA approved

Table 10 Patent Expiration Dates for submitted aBLA in the U.S. [54]

Active substance	**Biological medicinal product**	**Patent expiration date in U.S.**
Epoetin alfa	Epogen	August 2013
Filgrastim	Neupogen	December 2013
Pegfilgrastim	Neulasta	October 2015
Adalimumab	*Humira*	*December 2016*
Infliximab	*Remicade*	*September 2018*
Etanercept	*Enbrel*	*November 2028*

6. Potential reasons for the delay of the first biosimilar approval in the U.S.

6.1. Legal basis

Before the expiry of any patents/ data protection/ market exclusivity of biologicals, there was no urgent need for a legal pathway which facilitated the approval of similar biologic medicinal products.

In Europe for example, the first biologics lost patent protection in 2001 [75], and the legal basis for an abbreviated licensure pathway for biosimilars was created in 2004 with its first biosimilar approval for Omnitrope in 2006 [63]. Until 2013, only three different product classes of biosimilars were approved [75]. To date, 22 biosimilars of six different product classes were approved in Europe [63].

The patent landscape is difficult to oversee in the U.S., especially for biologics which are usually protected by several patents. Therefore, it is difficult to set a specific date when a biological loses its patent protection [71]. However, due to a missing legal basis for a regulatory pathway for biosimilars in the U.S. until 2010, some applicants already submitted their MAA of medicinal products which would have been considered as "biosimilar" in Europe through the available pathways, i.e. either by filing a full BLA under 351(a) of the PHS Act or by filing an abbreviated NDA under 505(b)(2) of the FD&C Act. The draft guidance for industry entitled "Applications Covered by Section 505(b)(2)" published in October 1999 states that the "FDA may accept an application submitted through the approval pathway described by section 505(b)(2) of the FD&C Act for a drug product containing an active ingredient(s) derived from natural sources or recombinant DNA technology" [39]. For example, an MAA for Omnitrope (active substance: somatropin - a recombinant growth hormone; reference product being Pfizer's Genotropin) was submitted under 505(b)(2) of the FD&C Act in June 2003 [35]. Several other growth hormone MAAs were granted market authorization on the basis of a full NDA under 505(1) of the FD&C Act. However, Omnitrope was the first recombinant human growth hormone receiving licensure through the abbreviated pathway under 505(b)(2) of the FD&C Act in 2006 [26]. The FDA took three years for granting MA for Omnitrope. In 2004, the FDA sent a letter to Sandoz stating that they are not able to decide on approval of this application due to scientific and legal issues raised in parts by different parties, e.g. Genentech Citizen Petition (Docket No. 2004P-0171), BIO Citizen Petition (Docket No. 2003P-0176), Pfizer Citizen Petition (Docket No. 2004P-0231), postponing its decision [41]. In its letter to Sandoz, the FDA announced to hold two public workshops - one in September 2004 and the other in February 2005 - addressing the requirements for demonstrating similarity of a protein product with regards to "manufacturing, characterization, immunogenicity,

preclinical and clinical studies, and efficacy surrogates" to a reference product licensed under the FD&C Act or the PHS Act [41]. However, as the reference product Genotropin sought licensure filing an NDA under the FD&C Act instead of applying for MA through a BLA under the PHS Act, Omnitrope was legally eligible to the abbreviated pathway according to the FD&C Act. Finally, Sandoz sued the FDA for not deciding on their application although the legal basis determined to either approve or reject an application within a defined timeframe [53]. On May 30th, 2006, forced by the court, the FDA finally granted MA for Omnitrope as therapeutic alternative and not as equivalent, i.e. not as interchangeable with its reference product Genotropin [42]. Interestingly, this FDA approval was granted shortly after Omnitrope was granted MA as the first biosimilar in Europe on April 12th, 2006 [63]. However, the FDA clarified that the approval of Omnitrope does not pave the way for approval of follow-on proteins of more complex nature or incompletely characterized proteins even though the respective reference products sought licensure under section 505 of the FD&C Act. Biosimilars to biologics approved under the PHS Act are not eligible to the abbreviated pathway under the FD&C Act at all [6]. So, the "Omnitrope case" can be regarded as the kickoff for realizing the necessity of an abbreviated approval pathway for biosimilars by the FDA.

Interestingly, in 2007 Janet Woodcock as representative of the FDA mentioned before the Congress that as a result of the public meetings held in 2004 and 2005 discussing legal and scientific aspects related to follow-on biologics, the FDA realized the need for guidance regarding follow-on biologics and therefore, the FDA is working on guidance documents regarding the approval of follow-on biologics under the FD&C Act [26]. However, these guidance documents were never published. Instead, the need for an abbreviated licensure pathway for follow-on biologics with reference products approved under the PHS Act was sensed and the preparation of draft laws emerged. In 2007/2008, four bills addressing an abbreviated approval pathway for follow-on biologics were introduced to the Congress [72]:

1) H.R.1038 (110th Congress)/ S.623 (110th Congress) - "Access to Life-Saving Medicine Act" - "Waxman-Bill" [67, 84];

2) H.R1956 (110th Congress) - "Patient Protection and Innovative Biologic Medicines Act of 2007" - "Inslee-Bill" [68];

3) S.1695 (110th Congress, 1st & 2nd Session) - "Biologics Price Competition and Innovation Act of 2007" - "Kennedy-Bill" [85, 86])[72].

4) H.R.5629 (110th Congress, 2nd Session) - "Pathway for Biosimilars Act" - "Eshoo-Act" [69]

These bills reflect the diverse interests of different stakeholders, e.g. with regards to data/ market exclusivity or patent issues [64].

Finally in 2010, the BPCIA of 2009 was enacted and the legal basis for biosimilar approval was established [81].

Looking at this time scale, it took the U.S. more than six years from recognizing the need for an abbreviated approval pathway for follow-on biologics to the final enactment of the respective law. The greatest challenge to create an abbreviated pathway for biosimilars was to meet the interests of all involved parties, e.g. of the innovators as well as the companies which develop the follow-on biologics. Extensive discussions had to take place to consider all relevant aspects and to achieve the best compromise for all involved stakeholders [64].

6.2. **FDA**

There are several factors responsible for the cautious behavior of the FDA regarding assessing and approving aBLAs.

First of all, the adopted law is very vague which causes a huge need for interpretation by the FDA, e.g. the extent of data required for an aBLA can be solely decided by the FDA. Although the law laid down the provisions for the general content of an aBLA, it is also stated that the detailed content is the FDA's responsibility to decide upon [81].

As the FDA was bound by BPCIA to consider public comments when drafting guidance documents [81] and in addition was lacking experience with assessment of aBLAs, it took the FDA some time until the first draft guidance documents were published. Interestingly, these first draft guidance documents were finalized after the first approval of a biosimilar medicinal product in 2015. It looks as if the FDA needed their drafted guidance to be proofed by passing through the approval process before they were able to finalize them (for details refer to section 3.3.3). The FDA is still in the process of learning how to handle the assessment of aBLAs including the process of drafting and finalizing required guidance for industry. These processes probably cause extensive internal discussions as well as discussions with the sponsors, which makes it difficult to estimate the actual required number of staff so that an enormous workload occurs for the FDA staff. When looking into the Fiscal Year 2014 performance report [33], the BsUFA related review workload for pre-submission meetings and meeting requests, procedural notifications and responses and application reviews increased from FY13 to FY14 by 41%, i.e. from 95 to 156. Some of the performance goals could not be met, e.g. scheduling BPD Type 2 meetings which are actually very important to the sponsor as the main objective of these meetings is the discussion of specific issues regarding the development program like study design or endpoints. The longer it takes for the sponsor to receive guidance from the FDA, the longer the development program will take which delays the submission process. It is to be expected that review workload increases continuously within the next few years because of the numerous ongoing BPD programs and as a result the expected numbers of aBLA submissions (refer to section 5). In addition, staffing resources were limited due to budget restraints in FY2013 and 2014 [33].

Furthermore, one has to consider that the cautious behavior of the FDA in terms of approval of biosimilars might be caused by the different litigation culture compared to Europe. Because of

easily facing lawsuits, the FDA has to be very thorough in assessing and approving biosimilars and therefore might request more additional information from sponsors than the EMA would probably do in Europe to finally grant MA to a "bulletproof" application.

In conclusion, one can say that design possibilities due to vague legal provisions, inexperience of the FDA regarding biosimilar approval, staffing restraints combined with increasing workload of the FDA, and the litigation culture in the U.S. have an impact on the slow progress in approving biosimilars in the U.S.

6.3. Potential Concerns

There are several issues which are being discussed or which cause concerns among the FDA, the public or the stakeholders regarding the new legal pathway for approval of biosimilars in the U.S.. These issues contribute - each to a different extent - to the retardation of the biosimilar approval process in the U.S. The following sections outline the main points.

6.3.1. Patent issues ("Patent dance")

In the U.S., patent litigations are common among innovators and generic companies as triggered by the Hatch-Waxman Act which laid down incentives such as a 180-day market exclusivity period for the first generic medicinal product which applies for MA, resulting in much patent litigation [92].

When designing the law for a biosimilar approval pathway, the patent issue was considered, resulting in explicit statutory guidance under section 351(l) of the PHS Act outlining how to handle patent issues prior to approval. This includes handover of confidential information to the innovator, including details of the manufacturing process and dealing with patent disputes (refer to section 3.1). For medicinal products licensed under the FD&C Act, patents are listed in the so-called "Orange Book" [38] which makes it easy for generic companies to check during development of a generic product if a patent might be infringed. The patents of biologics licensed under the PHS Act are not listed in the "Purple Book" which lists all licensed biological products including the respective biosimilar or interchangeable products [36] - the counterpart to the "Orange Book" for generic medicinal products. Section 351(l) of the PHS Act regulates the handling of patent issues between the innovator and the sponsor - commonly known as the "patent dance". It describes resolution of patent disputes and includes notification procedures including exchange of information, e.g. the disclosure of information on the confidential manufacturing and development processes of the biosimilar from the biosimilar sponsor and a list of the potentially infringed patents from the innovator. Patents which have not been disclosed to the biosimilar sponsor by the innovator during the "patent dance" cannot be asserted against the biosimilar sponsor later on [81].

After submission of Sandoz' aBLA of Zarxio, Sandoz did not disclose their MAA and the confidential data on the manufacturing and development process of the follow-on biologic to the

innovator, but instead just informed Amgen about the submission of their aBLA. For this reason, Amgen - the innovator of Neupogen - filed a lawsuit against Sandoz. However, Sandoz notes that the law as stated under 42 U.S.C. §262(l)(2)(A) ("shall provide to the reference product sponsor [...]") does not explicitly require the sponsor to disclose the data. It has been judged by the United States Court of Appeals for the Federal Circuit that this provision has to be looked at in conjunction with 42 U.S.C. §262(l)(9)(C) and 35 U.S.C. §271(e)(2)(C)(ii) which laid down the measures the innovator of the reference product can take in case the sponsor does not follow the provisions laid down under 42 U.S.C. §262(l)(2)(A) [93]. Another issue for which Sandoz was sued by Amgen is the minimum 180-day-notice to the innovator of the reference product before commercial marketing of the product as laid down under 42 U.S.C. §262(l)(8). Amgen argues that this period of time for notification only starts after MA has been granted by the FDA. The United States Court of Appeals for the Federal Circuit agrees with Amgen's arguments granting the innovator of the reference product an additional six months of marketing exclusivity [93].

Due to patent litigation, it can be expected that the placing on the market of the next biosimilars which gain licensure in the U.S. might be delayed for some time. The "patent dance" challenges the success of the biosimilar approval pathway because the sponsors might face several patent disputes and lawsuits which are a risk to their return of investment if they cannot place their biosimilars on the market.

6.3.2. Extrapolation

Extrapolation is one of the key issues causing concern regarding the approval of biosimilars in conditions of use which have not explicitly been tested in clinical studies. The provisions for extrapolation are laid down in the guidance on "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" [51]. Although extrapolation is one of the key issues being discussed, e.g. during the AAC meeting on Feb 9th, 2016 discussing the MAA of CT-P13 (infliximab) [31], it can be regarded as the main advantage of an aBLA because omitting clinical trials for additional conditions of use saves money and time for the sponsor. Because extrapolation is of such importance for the aBLA pathway, it is of major interest how the FDA is going to deal with extrapolation when it comes to rather complex products such as monoclonal antibodies. Therefore, looking back, the AAC meeting on 9th Feb 2016 discussing the MAA of CT-P13 can be regarded as a positive indicator for the acceptance of extrapolation by the FDA. The committee voted 21 'yes' against 3 'no' for recommendation of approval of CT-P13 in all requested conditions of use [31]. This vote of the AAC meeting can be regarded as a significant milestone in biosimilar implementation in the U.S. However, extrapolation was discussed in detail and can be regarded as the major issue, especially because Health Canada did not grant MA for the indications Crohn's Disease and Ulcerative Colitis - inflammatory bowel disease (IBD). In their opinion, it was not sufficiently demonstrated that the MoA was identical in all conditions of use licensure was sought

for - especially with regards to Crohn's Disease and Ulcerative Colitis, so that the assessment could not be positively concluded for these indications [66]. Although there might be different MoA in IBD, the sponsor of CT-P13 provided extensive data justifying that a second MoA in IBD does not play a major role in CT-P13 treatment. Therefore, most of the AAC members were convinced that the provided data and justification with regards to the totality of the evidence allow for extrapolation to Crohn's Disease and Ulcerative Colitis [31]. In addition, the FDA commented on the concerns about extrapolation that the basic idea of the newly established aBLA is extrapolation of indications which does not mean that safety of patients is disregarded. During assessment of an aBLA, one has to focus on the "totality of the evidence" and the "residual uncertainties" and decide on extrapolation and finally on granting MA by taking these concepts into account [30].

6.3.3. Substitution - interchangeability

Interchangeability is an important aspect in terms of biosimilar approval and subsequent success in gaining market share. The sponsor can submit an aBLA explicitly requesting interchangeability of their proposed product with the reference product. The first interchangeable product to its reference product will be granted one year of market exclusivity until another interchangeable product with the same reference product receives licensure. In case of ongoing/pending patent litigation, the duration of regulatory exclusivity might be adjusted [81]. The requirements for a successful aBLA of an interchangeable product are not yet defined by the FDA. However, a respective guideline is planned to be published [94].

As long as interchangeability is not determined by the FDA during assessment of an aBLA, the medicinal product cannot be regarded as therapeutically identical and therefore, the innovator's product cannot directly be substituted with the biosimilar product according to current legislation. The BPCI Act laid down that a biosimilar which has been granted MA as interchangeable with the reference product can be automatically substituted by pharmacists without confirmation by the prescriber [81]. However, in general, substitution of medicinal products is regulated at state level and the decision in terms of substitution lies with the State Boards of Pharmacies. Therefore, state laws regarding substitution of biologics with interchangeable or biosimilar biologic products are subject to innovator lobbying to prevent passing of the laws which regulate substitution of biosimilars [4]. Figure 5 gives an overview of the states which have already dealt with legislature regulating substitution of biosimilars.

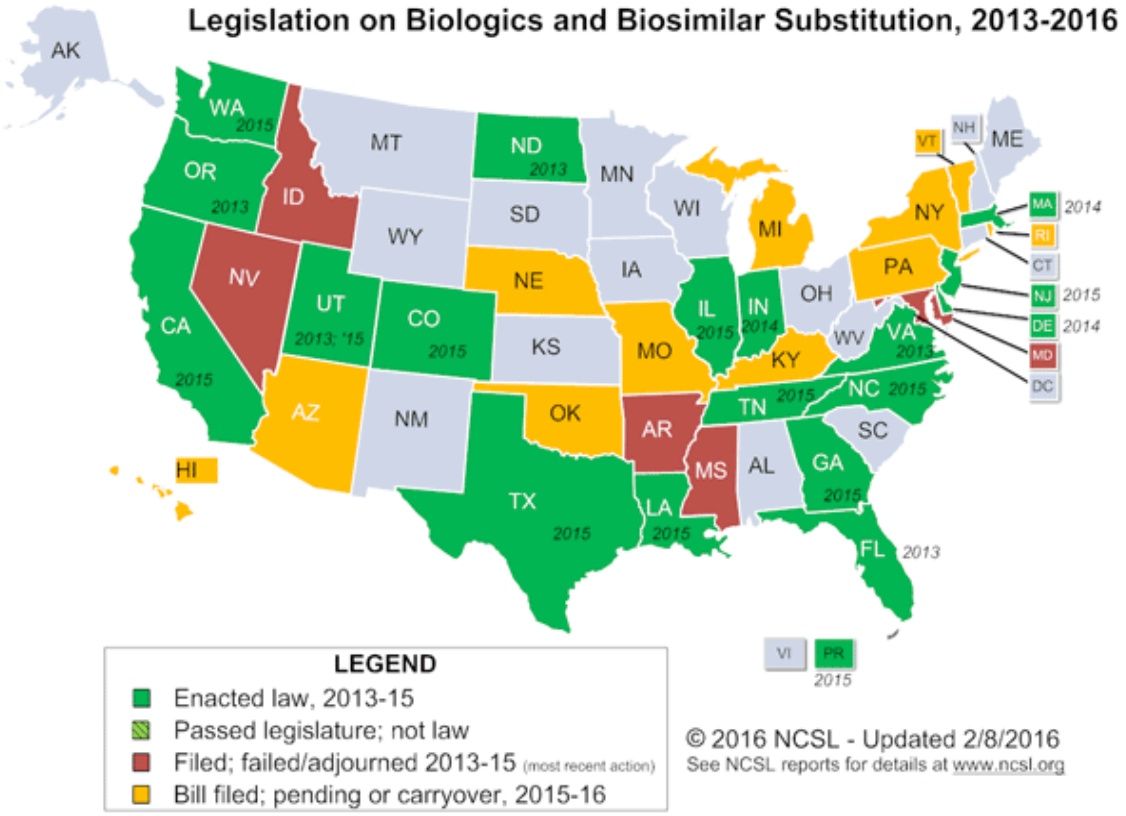

Figure 5 Overview of the states showing the status of the legislation on biologics and biosimilar substitution from 2013 - 2016 published by National Conference of State Legislature [7]

All enacted laws refer to 'interchangeable' biosimilar medicinal products. Most laws make provisions for the notification of the prescriber and/or the patient of the substitution. In addition, the prescriber can determine that the "brand medicinal product is medically necessary" which prevents substitution. In some states, records have to be retained about the substitution for a defined period of time and the State Board of Pharmacy is required to maintain and provide a current list of interchangeable biosimilar products [7].

Therefore, biosimilars which were not approved as 'interchangeable' by the FDA cannot be substituted for the reference product unless state laws are amended accordingly.

6.3.4. Immunogenicity

Another major safety concern regarding biosimilars is immunogenicity which can be influenced by patient related and product related factors [51]. The formation of anti-drug antibodies (ADA) may lead to a loss of efficacy. Hypersensitivity reactions, especially anaphylaxis, are a risk for the safety of the medicinal product [49]. If extrapolation of data obtained for one or several indications is applied to other indications licensure is sought for, the trepidation exists that potential safety risks might be overlooked. There have been some incidences in which the assessment of an MAA or of

post-approval changes to the medicinal product did not reveal major safety concerns, but caused severe reactions when finally marketed. For example, in the early years after 2000, after a change in the formulation of Eprex, an epoetin alfa, an increased number of pure red cell aplasia (PRCA) incidences was observed and was associated with the formation of ADA's to the medicinal product in patients with chronic renal failure [79]. The reasons for increased PRCA are not completely elucidated to date [79]. However, it demonstrates the complexity of biologics and the importance of thorough assessment of supposedly minor post-approval changes and of MAA for potential biosimilars. Another example occurred more recently. A new erythropoietin-stimulating-agent - Omontys (peginesatide) which was only approved in March 2012 [27] was withdrawn from the market in February 2013 due to the post-marketing reports of several incidences of severe hypersensitivity reactions including anaphylaxis which can be lethal to the patient [1]. It was described that the incidences of hypersensitivity reactions remained the same as observed during clinical trials (0.2%). However, the severity of the reactions post-approval was much worse than observed during the clinical studies and therefore, the product had to be withdrawn from the market because the risk-benefit ratio was no longer in favor for the benefit of the medicinal product [12].

These experiences in the past might trigger the concerns of the FDA of not detecting certain risks during assessment, making them very cautious in waiving clinical trials or in allowing extrapolation to other indications than clinical studies were conducted for.

6.3.5. Naming

There is a lot of discussion around the naming of biosimilars, which is another cause for concern with regards to acceptance and recognition by the users/prescribers or with regards to safety and pharmacovigilance of the biosimilars post-approval. There are concerns that biosimilars might cause different adverse events which should be appropriately linked to the respective product. Therefore, a distinctive name for biosimilars might be feasible [96]. It took the FDA a rather long time to decide on the naming of biosimilars. The most recently published draft guidance for industry by the FDA addresses exactly this issue - Nonproprietary Naming of Biological Products [52]. The FDA's current view on this issue is to add a unique suffix to the nonproprietary name of the biosimilar medicinal product to facilitate the differentiation of similar products, to avoid inadvertent substitution with the reference product or any biosimilar of the same active ingredient and to facilitate pharmacovigilance of each individual biological medicinal product including biosimilars [52]. The question remains if this approach is appropriate for interchangeable products. The FDA asks for comments on this matter because they have not come to a final decision yet [52]. This draft guidance document was only published in August 2015, so it took the FDA quite some time to settle on this matter which might have contributed to the delay of biosimilar approval in the U.S.

6.4. Conclusion

There is no “one reason” causing the delay of approval and placing on the market of biosimilars in the U.S. However, it looks more like several points have to be considered and add up to delaying the whole process. First of all, the need for an abbreviated pathway for biosimilar approval was noticed later than in other countries, e.g. in Europe, and therefore, the process of establishing the legal basis for an abbreviated pathway started later in the U.S. (refer to section 6.1). Due to the ‘litigation culture’ in the U.S., it is conceivable that the U.S. were rather cautious and wanted to learn from other countries which had already approved biosimilars. It is always easier to realize how to do things when looking at ‘mistakes’ made by others or considering challenges other parties had to face. Many different factors had to be considered first before respective guidance documents were published. As mentioned before, one gets the impression that the FDA is still in the process of consolidating their views on the requirements for an aBLA. The first finalized guidelines were published after the first MA approval of a biosimilar in the U.S., so that the draft guidance documents had to be proven right and could be amended according to the lessons learned from their first successful approval process.

However, there are still product class specific FDA guidelines missing that have been published by the EMA and that would be of great advantage to the sponsor in order to know from the beginning of the development program which data is needed for submission of a successful aBLA. Although stated in the BPCIA, no such product specific guidance documents were published by the FDA to date [81]. The FDA relies on a case-by-case recommendation about the data requirements for an aBLA which leaves a lot of flexibility and workload to the FDA. Depending on the experience already gained with the product e.g. in different countries than the U.S. and depending on the experience gained with the aBLA itself they can adapt the requirements. It is highly recommended that the sponsor is in close contact with the FDA from the early beginning of the development process and takes the opportunities offered by the BPD program, i.e. consultation with the FDA by requesting meetings to discuss the required data for a successful aBLA. It will take some time and probably several positively approved aBLAs until the FDA will have finally defined the assessment process for biosimilars. The FDA is in close contact with EMA through their ‘biosimilar cluster’ discussing their directions of biosimilar approval and learning from each other [15].

The question remains whether the biosimilar approval pathway has a future in the U.S.. Pointing out the hurdles a sponsor faces, e.g. lawsuits from the innovator caused by difficulties of the sponsor to oversee all patents that could be infringed, disclosure of confidential information to the innovator might result in less applications and approvals under 351(k) of the PHS Act. Instead, a sponsor might rather think about submitting a standard BLA (according to 351(a) of the PHS Act) to profit from the data and market exclusivity and to be able to get their data compared to a placebo. This allows for differences to the innovator’s product which includes superiority of the proposed product which would result in a market advantage over the innovator. However, this decision is not easy to

make and will depend on several factors, e.g. the complexity of the product, the scientific in-depth knowledge of the MoA supporting the granting of extrapolation and the simplicity to replicate the same PK/PD profile as the reference product. The extent of clinical studies will largely depend on suitable surrogate markers. In cases in which a clearly measurable endpoint is not available, e.g. for monoclonal antibodies, extended clinical data might be required for approval which causes extensive time and costs for clinical studies. Therefore, only certain product classes might be successful as biosimilar in the U.S.. The amount of required data, i.e. the duration and costs of development as well as the decision on extrapolation of conditions of use and interchangeability of medicinal products might determine whether it is worthwhile to apply under 351(k) of the PHS Act or rather to submit a full BLA (application under 351(a) of the PHS Act) to profit from the incentives offered by a full BLA. As for the abbreviated pathway for generics [92], it is expected to take several years until this new biosimilar approval pathway will be widely accepted and used by sponsors. The FDA as well as the sponsors have to get to know the challenges and chances of this pathway to gain the most out of it.

7. Outlook - regulation of “ATMP-similars”

Advanced Therapy Medicinal Products (ATMP) can be regarded as even more complex and challenging to regulate than other biologics. Therefore, the question arises if and how “ATMP-similars” might be regulated in future.

Looking back at the development of a biosimilar approval pathway in the U.S. reveals that the most important factor for starting off with the development of such a specific licensure pathway is the industrial need for it, i.e. unless the industry does have an urgent need for a specific licensure pathway, no-one will start drafting respective bills. Furthermore, the requests for guidance by industry/ sponsors on the requirements for a particular MAA indicate the need for guidance documents which have to be published by the regulatory agencies.

However, before considering the regulation of “ATMP-similars”, the question is:

What are ATMPs and how are they currently regulated in Europe and in the U.S.?

One has to mention that the acronym “ATMP” is commonly used in Europe and a respective definition is laid down in Regulation (EC) 1394/2007. The class of Advanced Therapy Medicinal Products (ATMPs) is complex and heterogeneous and consists of the following categories according to the definition of ATMPs laid down in Article 2(1)(a) of Regulation (EC) 1394/2007 - the legal and regulatory framework for Advanced Therapy Medicinal Products in the EU:

- Somatic cell therapy medicinal product
- Tissue-engineered product
- Gene therapy medicinal product

In Europe, MAA of ATMPs has to be filed through the centralized procedure in accordance with Regulation (EC) 726/2004. Nonetheless, an ATMP can be granted a national MA under certain provisions such as in case the product is patient-specifically prescribed by a physician and individually prepared in the same member state, the manufacturing occurs on a non-routine basis with set quality standards, and the treatment has to be applied in a specialized facility by a physician, and the provisions are laid down in article 28 of Regulation (EC) 726/2004.

In the U.S., the acronym “ATMP” is not commonly known. The respective products are defined in 21 CFR 1271.3(d) as human cells, tissues, or cellular or tissue-based products (HCT/Ps). HCT/Ps are regulated by the Office of Cellular, Tissue, and Gene Therapies (OCTGT) in the Center for Biologics Evaluation and Research (CBER) of the FDA. According to 21 CFR 1271.20, HCT/Ps which neither fall under 21 CFR 1271.10 nor under the exceptions listed in 21 CFR 1271.15 are licensed as biologicals under section 351 of the PHS Act. For the ease of reference, ATMPs and HCT/Ps are referred to as ATMPs in the following paragraphs. When explicitly referring to the U.S., HCT/Ps are mentioned.

When considering the licensure of “ATMP-similars”, two main aspects need to be discussed:

- Is a “similar” medicinal product conceivable for each class of ATMPs?
- Is a regulatory pathway already available and are specific guidelines already published?

Regarding the first aspect, one has to take into consideration that the development of a complex similar medicinal product largely depends on the expected return-of-investment (ROI). This might be impaired if the target population is small, e.g. in case of an orphan designation where it might be difficult to obtain sufficient and satisfying data for a MAA, and if the developmental costs are too high due to cost intensive clinical trials. If the extent of required data outweighs the potential benefits of an abbreviated pathway, the sponsor will not go for this pathway, but rather favor the submission of a full MAA, if any. Especially for the development of medicinal products with orphan designations, there are incentives for a sponsor to encourage the development of such medicinal products. Therefore it seems unlikely that an abbreviated pathway for “ATMP-similars” and the requirements set by the agencies will support the development of a follow-on ATMP to a reference product with orphan designation.

Another issue that questions the feasibility of “ATMP-similars” is the aspect that many ATMPs are developed to be autologous medicinal products, i.e. these medicinal products are patient specifically produced, e.g. ChondroCelect approved by EMA in 2009 [9]. So, these medicinal products are by themselves similar and not identical because every single patient has a different subset of cells which always results in a similar medicinal product. Therefore, it almost seems to be a philosophical question if there can be similar medicinal products of patient specific products. This leads to the importance of the statement “The process is the product” as often used in the context of biosimilars. The manufacturing process can be regarded as the core element of a product in case of rather complex medicinal products such as biologicals and ATMPs. When discussing a potential approval pathway of “ATMP-similars”, one has to take into consideration the special requirements regarding the manufacturing process, even though it needs to be discussed if an abbreviated approval pathway can solely rely on the manufacturing process. This seems unlikely with the current stage of scientific understanding of the requirements for regulatory approval of medicinal products. Therefore, one has to wait for standardized off-the-shelf ATMPs, e.g. like allogeneic chimeric antigen receptor (CAR) T cells for the targeted treatment of cancer which can be thoroughly characterized and controlled, and therefore, might be of interest to sponsors for the development of an “ATMP-similar”. However, such ATMPs are not even close to marketing.

Regarding the second aspect, one has to differentiate between Europe and the U.S. In Europe, ATMPs are regulated according to Regulation (EC) 1394/2007. As laid down in provision (2) of Regulation (EC) 1394/2007, ATMPs “are biological medicinal products within the meaning of

Annex I to Directive 2001/83/EC”, i.e. that article 10(4) of Directive 2001/83/EC which is the legal basis for the abbreviated biosimilar approval pathway, also applies to ATMPs. In the U.S., as outlined before, the HCT/Ps are licensed as biologicals under section 351 of the PHS Act and therefore the abbreviated pathway for biosimilar approval under section 351(k) of the PHS Act would also be eligible to “HCT/P-similars”. It appears that there is no real need for an individual legal basis for the regulation of “ATMP-similars” as they are mainly covered by existing directives.

There are no specific guidance documents regarding “ATMP-similars” available to date and as mentioned before, it is unlikely that there will be any such documents until the industry/sponsors clearly declare their needs for guidance on “ATMP-similars”. This need will occur at the earliest when the patent protection/ data or market exclusivity of relevant ATMPs expires. As ATMPs are only slowly entering the different markets, it will most likely take several more years until “ATMP-similars” are discussed with the regulatory agencies in detail.

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9. List of Figures

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Eidesstattliche Erklärung

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

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Unterschrift