The Issue of Extrapolation of Indications in the Registration of Biosimilars

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List of Abbrevations

ACR20	American College of Rheumatology 20% response
ADA	Anti-drug Antibody
BGTD	Biologics and Genetics Therapies Directorate *(at Health Canada)*
BPCI Act	Biologics Price Competition and Innovation Act *(USA)*
CD	Crohn's Disease
CHMP	Committee for Human Medicinal Products (EMA)
ECCO	European Crohn's and Colitis Organization
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPAR	European Public Assessment Report
EWP	Expert Working Group (ICH)
EWP	Extrapolation Working Group (EMA)
FDA	Federal Drug Agency (USA)
GRIP	Global Research in Paediatricss – Network of Excellence
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMID	Immune-mediated inflammatory diseases
IPRF	International Pharmaceutical Regulators Forum
KFDA	Korean Federal Drug Agency
M&S	Modelling and Simulation
mAB	Monoclonal Antibody
MSWG	Modelling and Simulation Working Group *(EMA)*
PBPK-modelling	Physiologically-based pharmacokinetic modelling
PD	Pharmacodynamic
PDCO	Paediatric Committee *(EMA)*
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency (*Japan*)
PREA	Pediatric Research Equity Act *(USA)*
PsA	Psoriatic Arthritis, Psoriasis-arthritis
Q&A	Questions and Answers
RA	Rheumatoid Arthritis
RBP	Reference Biotherapeutic Prodcut
RCT	Randomized Controlled Trial
RP	Reference Prodcut
SAWP	Scientific Advice Working Party (*EMA - CHMP)*
SBP	Similar Biotherapeutic Product
SEB	Subsequent Entry Bbiologic (*Canada)*
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
WHO	World Health Organisation

1. Introduction

The first biosimilar drug has been approved by the European Medical Agency a decade ago. Initially, however, they were of interest mainly for biotechnology experts and their respective regulatory counterparts. Only in the last two years did they take center stage in more general health-care related discussions. They evoke a number of intensely debated issues, involving stakeholders from both academia and industry, regulatory authorities and medical learned societies, health-care providers, patient organisations and others. The aim of this Master Thesis is to introduce and analyse one of the most prominent of these current biosimilar-related issues, namely the regulatory framework and scientific rationale for the extrapolation of indications.

Biosimilars are similar, yet not fully identical copies of biological drugs. They compete with biologicals that have run out of patent. The first biologicals that ran out of patent in Europe belonged to the therapeutic classes of human growth factors, erythropoietin, and granulocyte colony-stimulating factors (G-CSF). They are used to treat relatively few patients and thus represent rather small markets. Even if 14 biosimilars in these three classes had been approved in the European Union in 2010, by 2011 they still accounted for less than one percent of the total sales of biologicals in the EU [Blackstone 2013]. This situation began to change in 2013 with the approval of the first monoclonal antibody biosimilar in the EU. Its originator product infliximab is an inhibitor of TNF-α and belongs to the ten top-selling drugs of the world since many years. The biosimilar of infliximab was launched in Europe in 2015. It is expected to gain a considerable market-share in the long run. This is one reason for the recently increased interest for biosimilars.

The perception that biosimilars are bound to become commercially attractive, is augmented by the approval of the infliximab biosimilar by the FDA in April 2016 – the second biosimilar that will be available in the United States at all after a copycat version of the G-CSF drug filgrastim had been approved as the first biosimilar in the US in 2015. The fact that the FDA is about to close the nine-year time gap on the EMA in terms of the approval of biosimilars obviously stirs up the attention of many stakeholders of the health-care system. This is the second reason for the recently increased interest for biosimilars.

The third one overlaps with the first and is triggered by anticipation. Within the next six years, most major patents on some of the world's best-selling biologicals will expire, including not only TNF-α inhibitors for the treatment of immune-mediated inflammatory diseases, but also many monoclonal antibodies with an oncological indication, which have considerably improved the treatment of certain tumors [Bressler 2015]. Until 2020 alone, biologicals with estimated sales of 100 billion US-Dollar will run out of patent [Blackstone 2013].

The competition of biosimilars with these biologicals is expected to lead to substantial price decreases, both for the copycats and for their originators. This is important for two reasons:

Biologicals are effective. Some of them, especially monoclonal antibodies, have revolutionized medicine and helped treat or even cure diseases that were difficult if not impossible to treat before, namely in rheumatology and in autoimmune diseases in general. In oncology, they can help to prolongue the life of cancer patients significantly. Price reductions will improve the affordability of biologicals and thereby increase access to them. Globally, 50 distinct biosimilars are currently in development [IMS 2016].

Biologicals are expensive. The average daily cost of a biological in the United States is 45 US-Dollar compared with only 2 US-Dollar for chemical small-molecule drugs [Blackstone 2013]. The global market for biological medicines therefore is projected to exceed 390 billion US-Dollar by 2020, which at his time would account for approximately 28% of the value of the entire global market for pharmaceuticals. Price-reducing competition by biosimilars thus will help to decrease healthcare costs worldwide considerably. The potential savings to health care systems in five EU key markets and the US alone are estimated to add up to 50 to 100 billion Euro during the next five years [IMS 2016].

Access, affordability and cost reduction belong to the issues which are currently intensively discussed with regard to biosimilars. Another important topic concerns interchangeability, i.e. the question, whether and by whom an original biological may be substituted. In this regard, the legislative and regulatory framework in the US and in Europe is different. Another issue, which is under discussion and unequally judged by different regulatory authorities, concerns the nomenclature of biosimilars so that they can be distinguished from their originators not only by their brand names but also by their INN names.

These are issues, however, which are not on the agenda of this Master Thesis. Some of them are being dealt with in other master theses. Rather, this thesis focuses on the issue of extrapolation of indications. At first, in chapter 2, the general concept of extrapolation in regulatory review will be introduced. The chapter explains why and in which applications extrapolation is frequently used in regulatory practice. It describes the initial emphasis on extrapolation in paediatric development plans, which more recently have led to attempts, mainly in the EU, to define a general framework and reliable algorithm for extrapolation in all areas of drug development, including the extrapolation of indications for biosimilars.

Chapter 3 gives an overview on the development, status and perspectives of regulatory thinking about the extrapolation of indications for biosimilars. For this purpose, it first defines the reasons that discriminate biosimilars from making use of the abbreviated application route for generics. It then explains why even originator biologicals need to undergo thorough comparability exercises to ensure their consistent quality and efficacy and why consequently the application dossier of a biosimilar must be much more comprehensive than that for a generic drug. Based on that, an account of the regulatory guidance in the EU with regard to biosimilars is given, focusing on provisions for the extrapolation of indications and detailing the most important

topics from the recent revisions of the biosimilar framework. This is amended by a view on WHO guidelines and regulations in other key countries.

These more theoretical considerations are in chapter 4 then illustrated by the example of the first monoclonal antibody biosimilar whose approval for all indications of its originator infliximab by the EMA (and other regulatory authorities) led both to disagreements with some other regulators (namely Health Canada) and to severe concerns of clinicians. In this context, the specific issues at stake – mode of action, pathophysiological differences, sensitivity of the pivotal clinical study's indication – are discussed as well as the problem of switching treatment of patients form the originator to the biosimilar infliximab.

2. The general concept of Extrapolation in regulatory review

2.1 Definition

Extrapolation is an established procedure in regulatory practice. In principle, it follows the insight that one needs not and should not reinvent the wheel time and again, but rather make meaningful use of already known data and facts, of their underlying correlations and of the results of related modeling and simulation outcomes.

Originally, the term extrapolation derives from mathematical sciences and means "to estimate (a value of a variable outside a known range) from values within a known range by assuming that the estimated value follows logically from the known values" [thefreedictionary-www]. In the context of medicine development it is defined with regard to efficacy and safety evaluation as "extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modification, number of patients required) to reach conclusions for the target population, or condition or medicinal product" [EMA/129698/2012], or in short: Extrapolation refers to the application of an empirical rule beyond the field in which it has already been proven or validated.

2.2 Use of extrapolation

Use of extrapolation principles is not uncommon. Most prominent in the field of drug development and authorisation processes are the approaches to extrapolate – fully or partially – from adults to one or more paediatric age groups according to the requirements in paediatric investigation plans (PIPs). However, extrapolation is necessarily and implicitly also involved in many other stages of drug development, where conclusions from specifically gained data are drawn to extend their validity to a more general scope. Examples for stages of drug development in which such extrapolations occur include [EMA/129698/2012, Komi 2014]:

- evaluation of stability data,
- comparability exercise in the assessment of manufacturing changes of biologicals,
- toxicity and carcinogenicity studies at early preclinical stages,
- conclusions between species in general, with regard to efficacy and safety evaluations especially from animals to humans with an emphasis on the first-in-man use,
- conclusions from the results in healthy volunteers to patients,
- conclusions between population subsets with regard to age, ethnicity, gender and pregnancy, renal or other relevant impairment, comorbidities,
- determination of dosages and administration modes and schedules,
- evaluation of safety and efficacy in different disease subtypes or stages or even also between different symptoms or diseases,

- evidence statements on different drugs with the same mode-of-action or within the same therapeutic class or even between therapeutic classes (this includes the assessment of biosimilarity without a comparative efficacy study).

In this perspective, even bringing an approved medicine to the market may thus be regarded as the result of kind of an unstructured extrapolation, because the patient characterisation in clinical praxis differs from the population, which was studied during the drug's development in terms of gender, age, co-morbidity, co-medication and so on. The legally required mandatory post-authorisation measures, e.g. close drug-safety monitoring, regular submission of benefit-risk evaluations and the critical re-assessment of approvability in a renewal procedure can thus be seen as the necessary validation and confirmation through the gathered post-approval experience in this special setting.

The reasons to apply extrapolation approaches in the clinical development process of medicines are manifold. In first line, they aim to avoid unnecessary studies due to financial reasons or in order to allocate resources as effectively and efficiently as possible. In this regard, extrapolation may contribute to the acceleration of the drug development process. Moreover, the number of healthy volunteers or patients enrolled in clinical studies should be kept as small as possible for ethical reasons. And finally, the question of feasibility has to be addressed; in special situations the possible scope of clinical studies is generally restricted by a low number of available patients or the nature of their disease (e.g. in orphan indications, or in extremely vulnerable patients). In these cases, a thorough and careful application of extrapolation principles enables investigators to draw meaningful conclusions from the limited evidence provided from their target population.

2.3 On the way to a general extrapolation concept

In principle, every extrapolation approach consists roughly of the steps **Concept – Plan – Validation,** which means more specifically:

- Determination of the problem and justification, why extrapolation may be considered to be applicable according to sound scientific reasons;
- Thorough assessment of the underlying principles, which build the rationale for extrapolation assumption;
- Compilation, evaluation and selection of existing data (e.g. from previous studies and established knowledge);
- Evaluation of uncertainties (which may occur across the whole process) and management thereof, consideration of risks;
- Decision, whether a full or partial extrapolation approach is applicable and whether additional data should be known;
- Evaluation and selection of appropriate tools (e.g. simulation and modelling approaches, statistical models);
- Iterative appropriate validation of the concept and its results;
- Mitigation of uncertainty and risk by appropriate follow-up measures.

Figure 1 Male

It is thus easily understandable that the more scientifically well founded source data is available, the less assumptions – and extrapolation - are needed.

By nature, extrapolation is implicitly inherent in scientific reasoning in general as it is in regulatory decisions. So, it comes as no surprise that regulatory bodies have been attempting to lay down general rules in order to establish more general standards and make decisions reproducible. The examples described below try to summarise the respective development of regulatory thinking.

Discussions from the early 1990s regarding the applicability of clinical data in order to prevent duplication of clinical trials resulted in the FDA Effectiveness Guidance [FDA 1998] and the tripartite ICH E5 Guideline Ethnic Factors in the accessibility of foreign clinical data [ICH 1998]. This Ethnicity Guideline provided a regulatory framework for the evaluation of the potential impact of ethnic factors, which may influence the acceptability of foreign clinical data, and described the requisitions for bridging studies, if required. In the Effectiveness Guidance, the FDA further detailed the new paradigm of drug approval as provided by the Food and Drug Modernization Act (FDMA) [US Congres 1997, Lee 2015], which requires "data from one [sic!] adequate well-controlled investigation and confirmatory evidence". Thus, the scientific progress in the understanding of the causal mechanisms of drug actions was well acknowledged, and a substantiated PK-PD relationship supported by a PK study will suffice for the approval of a new dose, regimen, dosage form or even a new, closely related indication of an already marketed drug.

In the same decade, the concept of extrapolation of efficacy data from adults to the paediatric population was introduced and defined in the US Labeling Rule for the first time [FDA 1994] in order to maximize the use of already existing evidence in paediatric drug investigation and development plans and minimize the number of children to be enrolled in clinical studies. According to this rule, the following main assumptions must be fulfilled for accessibility of children to drugs whose efficacy has been proven in adults:

- similar disease progressions
- similar responses to intervention
- similar exposure-response relationship

in the adult source population and the target paediatric population.

The principles, when and how either complete or partial extrapolation of study results from relevant prior clinical studies in adults may be appropriate, have subsequently been summarized in the often quoted "Paediatric Decision Tree Integration of PK-PD", which was published as an appendix to the FDA guidance for studying exposure-response relationships in 2003 [FDA 2003]. Advancements in the fields of modeling and simulation, pharmacometrics and biostatistics in general have been taken into account in the more recently (2014) drafted FDA guidance on general clinical pharmacology considerations [Burckart 2015, FDA 2014a] and resulted in accordingly adapted decision algorithms ("decision tree") for the planning of paediatric studies.

Generally, it has to be recognised that international collaboration and exchange has always been an important concern and priority of regulatory activities, especially in the US and in the European Union. Thus, the ICH E11 guideline on clinical trials in children [ICH 2000], which can be regarded as the first joint regulatory action in this respect, was implemented as well in the US as in Europe in the year of its finalization 2000 [www.ICH.org]. The extrapolation of data between regions and from adults/older paediatric patients to younger target groups is explicitly encouraged. Regarding the extrapolation between age groups similar provisions as in the 2014 drafted FDA guidance are defined; namely that the same indication is concerned, the disease progression is similar, the outcome of the concerned therapy is likely to be comparable, and the concentration-efficacy ratio matches. Moreover, emphasis is drawn to the PK/PD approach and the possible necessity to "develop, validate and employ different PD endpoints" and/or alternative PD assessments.

Currently, an addendum to ICH E11 related to extrapolation of data is under preparation because considerable progress has occurred since its first adaption. According to the final concept paper [ICH 2014], "it is acknowledged that there are differences in how regulatory authority define extrapolation and consider limitation of extrapolated data", but it is foreseen to provide informative reference to current regulatory thinking. Furthermore the concerned expert working group at ICH recommends the development of a harmonised guidance on the extrapolation of efficacy data in the near future, which should reflect namely the progress evolving from modeling and simulation approaches involving various methods as for example pharmacometrics, systems pharmacology, physiologically-based pharmacokinetic modelling and other mathematical/statistical approaches.

This reflects also very well the current regulatory thinking in the European Union. Use of extrapolation was more or less a case by case decision and laid down sparsely, too. Not least driven by the paediatric regulations evolving in the 1990s, European regulators focused on the challenges in extrapolation from adults and across age groups. Besides the adaption of the already mentioned ICH E11 guidance the importance of pharmacokinetic data supporting the extrapolation of efficacy across age groups was described in a particular guideline [EMEA/CHMP/EWP/147013/2004]. In workshops on modelling, the EMA sought exchange with external experts from international regulatory bodies, academia and industry, not only referring to the application in the paediatric setting, but also aiming to understand how the integration of compound specific and mechanistic and disease area relevant information into drug development programs could be harmonised. Thus, the Extrapolation Working Group, which had been established by the Paediatric Committee (PDCO) in 2009, consequently collaborated soon in particular with the Modelling and Simulation Working Group (MSWG) and the Biostatistics Working Group as well as the Scientific Advice Working Group (SAWP) in drafting an conceptual framework for all aspects of extrapolation [Male 2013, Skottheim Rusten 2014, Manolis 2013].

As a first step on the way to a more general framework for extrapolation approaches the so called "Concept paper" goes beyond the documents mentioned before and discusses "the possibility to develop an expanded and refined algorithm for extrapolation in all areas of medicine development" [EMA/129698/2012-Draft]. The paper asks to establish a structured and systematic approach to be followed when applying extrapolation exercises, starting with the determination

"i) when, ii) to what extent, and iii) how extrapolation can be applied".

Thus, decision making at regulatory bodies should finally be facilitated in a standardized manner. According to the authoring Extrapolation Working Group the next step in the direction to the final goal of a general guidance on the application of extrapolation in medicines development will put emphasis on the model situation in paediatric medicines development and it is suggested to develop a corresponding Reflection paper thereof. Setting up a database of case examples is a further recommended step, which was unanimously endorsed in all related comments received during the consultation.

Very recently, the designated "Reflection paper" has been published and discussed in an open workshop at EMA [EMA/199678/2016-Draft]. The detailed framework provided in the Reflection paper sets out a structured approach to be followed in therapeutic areas and specific situations, such as dosage optimisation for example, for which extrapolation is not yet mentioned in specific therapeutic guidelines. The paper details key aspects to be taken into consideration with regard to pharmacology, disease manifestation and progression as well as to clinical responses in both the source and the target population when creating an extrapolation plan, which will be part of the PIP. Again, it suggests "underlying principles may be extended to other areas of medicine development" [EMA/199678/2016-Draft].

Interestingly, the FDA makes a different use of the term "extrapolation" in the BPCI Act and in the context of PREA. In the context of BPCI "extrapolation" is used in the sense of extrapolation of indications in the licensure of a biosimilar. According to FDA this should not be mismatched with the use under PREA, which concerns the extrapolation between age groups. As US legislation requires that a proposed biosimilar drug must comply with PREA standards on its own, when taking into account the labeling of the reference product related to the condition licensure is seeked for, this issue of possible mismatching seems to be only relevant in the US. It remains to be seen, whether the FDA will also undertake efforts to develop a more general concept of extrapolation that will harmonize currently different definitions and thus avoid conflicts of interpretation.

2.4 Transfer to the extrapolation of indications for biosimilars

Some comments received during the consultation on the concept paper proposed to include reference to the extrapolation exercises already undertaken in the biosimilar approach. EMA answered that ”detailed guidance on extrapolation with respect to biosimilar products is best handled in specific guidance to ensure coherence with the body of guidance on the development of biosimilar medicinal products”, but assured that a close consultation with the biosimilar medicinal products working party will ensure compatible results of both expert groups.

Even if the current efforts in developing a more general guidance on the application of extrapolation in the regulatory contexts focus primarily on extrapolation across age groups in the paediatric setting, the principles can clearly be adapted to the extrapolation of indications in the registration of biosimilars.

As already mentioned, the common main **rationale** is to avoid unnecessary studies, both due to ethical and to economic reasons. The latter is especially important as clinical studies, which would otherwise have to be performed in every single indication applied for, are the most cost-intensive and time-consuming phases of drug development.

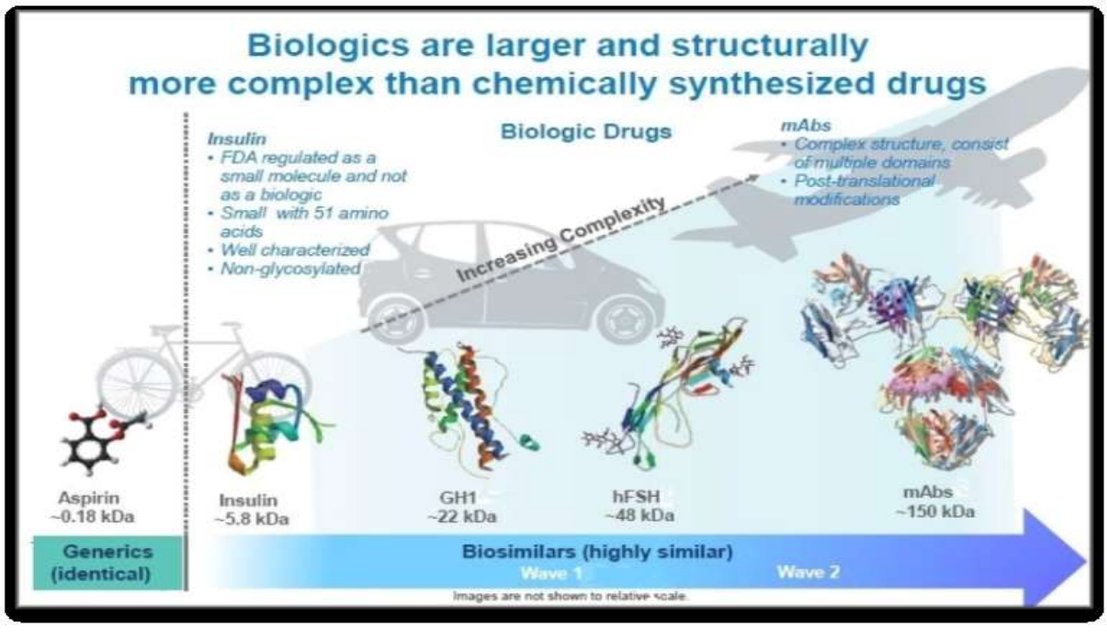
The determination of the problem addresses the questions, whether the involved drugs (originator and biosimilar) as well as the indications in question are essentially similar or follow essentially comparable mechanisms in order to extrapolate. Considerations, where and which problems may arise are undertaken at this step, too. This is already in close relationship to the assessment of underlying principles. Hence, the critical attributes, on which the proof of similarity is based, including the results from functionality assays and clinical evidence, will be scrutinized again. The target receptors and pathophysiological mechanisms involved in the source and the target indication will also be closely cross-checked with regard to possible differences, which might become meaningful as well as the patient cohorts typical in both indications. The overall knowledge gathered with the originator product, from the comprehensive similarity exercise and from external sources will be evaluated as to indicate, whether and which additional studies are necessary, resulting in the extrapolation plan. Of course insight gained will influence the study plan at every step. Iteration is indispensable.

3. Extrapolation of indications for biosimilars

3.1 Generics versus biosimilars

According to the principle of free markets, copycat versions of lucrative goods usually enter the markets as soon as exclusivity rights expire. This also occurs in the case of medicinal products. The resulting competition and price reduction is an officially appreciated consequence because patients are offered more affordable medicines and the pressure on healthcare budgets is reduced. Mandatorily, these copycat versions of medicines also need to proof safety and efficacy in order to get approved. In the case of active pharmaceutical substances, which consist of small, chemically synthesized molecules, only the chemical identity and bioequivalence of the generic drug to the originator product need to be demonstrated according to international regulatory standards. Thus, the application must include the quality part of the dossier and an regulatory abridged clinical part with only limited confirmatory clinical trials in order to demonstrate bioequivalence. Large, expensive and time-consuming pivotal confirmatory trials to demonstrate safety and efficacy in every concerned indication are not requested. Usually, terms and conditions of the granted license, including all approved indications are identical to the originator, unless single indications are still protected by exclusivity claims. [Dunne 2013]

It is obvious, that this abridged application and the waiving of clinical trials are essential for bringing cost-effective generics to the market. But with the advent of biological medicinal products the paradigm of an "identical" active ingredient of the originator and the copycat drug is no more suitable, as biologicals (also called biological drugs or biopharmaceuticals) differ substantially from small molecules (see table 1), comparable to the difference between a bicycle and an airplane, as figure 2 (adapted from AMGEN) illustrates.



Biological drugs usually derive from biotechnological production involving living organisms and recombinant technology, but may also be purified from natural sources. Most biologicals are proteins by nature. Their complexity ranges from relatively small peptides such as human insulin over small proteins like erythropoietin and reaches the highest grade with monoclonal antibodies or fusion proteins. Moreover, the grade of complexity goes along with a certain product-intrinsic heterogeneity, which may depend on post-translational glycosylation, terminal cleavage and/or modification, pattern of oxidation and deamidation and is highly dependent on external influences, i.e. changes in temperature. It is self-explanatory that changes in the manufacturing very likely may alter the properties of a given biologic product.

	Small-molecules	**Biologics**
Size	small: low molecular weight	medium to large: high molecular weight (up to ~10^3 fold larger than small molecules)
Structure / Complexity	simple: homogenous well-defined structure	complex: mixture regarding multiple levels of structure and posttranslational modifications e.g. glycosylation pattern (microheterogenicity)
Manufacturing	chemically synthesized, predictable and fully reproducible, approx. 50 in-process tests	primarily produced in living cells (unique cell line), complex manufacturing process, approx. 250 in-process tests
Characterization	full analytics (relatively) easy possible	difficult to fully characterize due to a mixture of related molecules (microheterogenicity)
Stability	relatively stable	mostly sensitive to storage and handling conditions
Route of administration	mostly oral	usually parenteral
Immunogenicity	low risk	high risk

Table 1 Differences between small molecules and biologicals

Taking into consideration this inherent variability of biologicals, which substantially depends on their origin from a living cell and the particularities of the manufacturing process - minor modifications may result in major product alterations - a sophisticated physicochemical and functional characterization of the biological product is extremely important in order to garantue that the product quality remains consistant over time. The significance of these critical quality attributes is taken into account by the regulatory authorities. They demand an elaborated choice of specification parameters as well as a thorough evaluation of the impact of changes in the manufacturing process in order to ensure that the quality, efficacy and safety of the product are not affected adversely; following the basic paradigm "the process is the product". The standards of the so called "comparability exercise" are laid down in ICH Q5E, which is globally enforced [ICH 2004]. The comparability exercise comprises all "activities, including study design, conduct

of studies, and evaluation of data that are designed to investigate whether the products are comparable". Remarkably, ICH Q5E stresses the concept of *similarity* instead of *identity.* It outlines that the compared quality attributes cannot be expected to be exactly identical, but rather only highly similar.

The comparability exercise is performed step-by step. It starts with the careful consideration of all "foreseeable consequences for the product" with regard to subsequent manufacturing steps, intermediates and related quality parameters and acceptance criteria. It weighs the criticality of each process step in relation to the complexity of the product. It then defines criteria, which are relevant for the assessment of similarity. Subsequently, it determines the studies to be performed and the data to be tested. In accordance with that, suitable analytical methods and biological assays, including (re-)validation necessities, are chosen. The most important quality parameters, which normally need to be assessed comprise: Physicochemical characteristics, biological activity, quantity, stability study results including knowledge about degradation products, purity and impurities, contaminants, as well as immunochemical properties.

Comprehensively collected quality data of the pre- and post-change product will then be analyzed and compared to determine, whether or not further confirmatory non-clinical or even clinical studies are necessary.

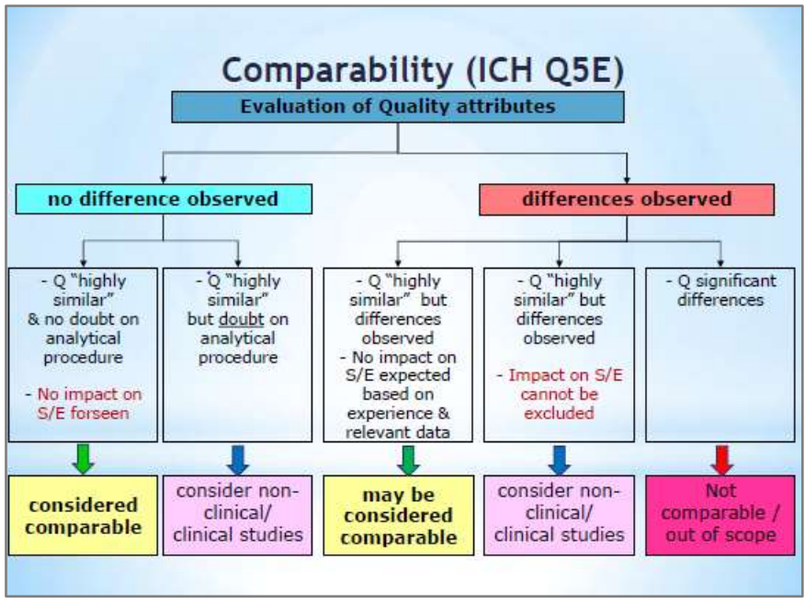


Figure 2: Comparability according to ICH Q5E (Brake)
Q = quality, S/E = safety and efficacy

Decisions on the extent of the comparability study program will be taken case-by-case, depending on the overall evidence and in accordance with product specific guidance, if available (as it is for instance the case for monoclonal antibodies) [EMA Guidance]. Looking at the comparability exercise from a European regulators' perspective, it is noteworthy that clinical studies, if they were required at all, so far needed to be performed only in one single indication

and have always been acknowledged in all valid indications based on the provided evidence of comparability [Weise 2012, Weise 2014].

If already the original biological drug bears a certain inherent variability as described before, this will all the more be true when comparing an original biological with its biosimilar, which in principle is the equivalent of a biological medicine's generic drug. The feedstock and the starting materials, respectively, and the manufacturing process of the originator and the biosimilar product will never be entirely identical –, not least because the manufacturing process of the biosimilar in general is deduced by "reversed engineering": Whoever wants to produce a biosimilar medicine must come from a detailed physicochemical analysis of the already marketed originator product and from there conclude backwards to the single steps of its synthesis before he can start to imitate them. [Bressler 2015]

Based on that, it is obvious that the application file for the licensure of a biosimilar needs to be much more comprehensive and detailed than the file for a small-molecule generic drug. The standard generic approach consists of the demonstration of bioequivalence and chemical identity with the small-molecule originator. This is definitely not sufficient to demonstrate biosimilarity. At any rate, the variability in the biosimilar must not be greater than in the innovator product itself. This means, that the amino acid sequence of the molecules must be identical and that with regard to microheterogenicity and post-translational modifications only small discrepancies are acceptable. The similarity has to be proven through an extensive analytical comparison program on the structural and functional characteristics, which assesses on one hand the product intra-inherent variability and on the other hand the inter-product comparability with the reference product. Basically, the same scientific principles that are in place to proof the comparability of biological products before and after manufacturing changes are applied here. Moreover, the complete proof of biosimilarity will necessarily also follow a stepwise approach. Any difference found in the follow-on biological will have to be justified. Its potential consequences will have to be monitored in the further product-tailored non-clinical and clinical study program. In general, the extensive non-clinical investigations, especially the in-vitro functionality assays, including the toxicity evaluation, must demonstrate a similar biological activity as the main basis for the assumption that the efficacy and safety of the follow-on product are similar to the original biological medicine.

The results from these in-vitro tests and assays serve as determinants, whether non-clinical in-vivo studies are required at all. The overall design of the clinical study program then will depend on the insights gained so far and will particularly address the issue of immunogenicity. Pharmacokinetic studies in a sensitive and homogenous population and PK/PD studies are usually requested to precede larger efficacy and safety comparative studies. However, it is generally assumed that the clinical benefit of a biosimilar has already been sufficiently verified

by the originator. The biosimilar development program is therefore aiming to establish (bio-) similarity to the reference biological drug and not clinical efficacy. Thus, the biosimilar must per definition prove to be as effective as – or non-inferior to – the reference drug, but may never be of superior efficacy. After having proven evidence of biosimilarity by the comparability exercise and by demonstrating clinical efficacy in the most sensitive indication, the extrapolation of indications should be justified by sound scientific reasons.

The documentation to be presented with the application for the licensure of a biosimilar hence substantially differs from the documentation, which regulatory authorities request for either generics or originator biological drugs. The analytical part and not the clinical part dominates in the application file for a biosimilar. It has to be very comprehensive as the analytical investigations are head-to-head comparisons of the biosimilar and its reference originator.

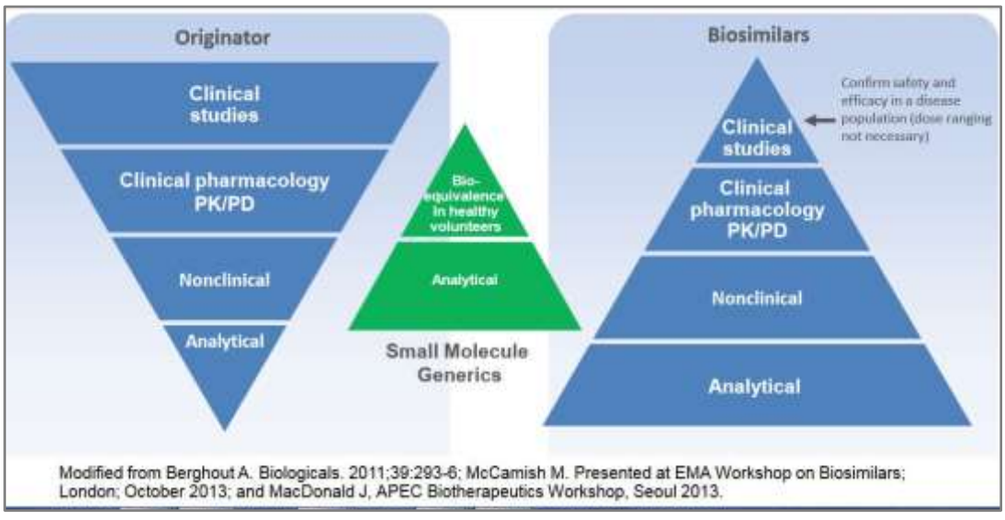


Figure 3: Dossier requirements for originator, small-moleculare generic, and biosimilar drug

As a consequence, the development times (8–10 years) for a biosimilar are shorter and its development costs lower (approx.. $ 150-250 Mio.) [Blackstone 2013]. This represents an economic stimulus when compared with the development of an original biological drug, which may last 10–15 years and costs approx. $ 1.2 billion (including failure costs) [PhrMAorg 2013]. In this regard, it is definitively essential for a biosimilar producer to gain the approval of all indications of the originator drug. Otherwise, the biosimilar's economic potential could only marginally unfold and the incentive to develop, produce and market a biosimilar drug would be far less. Moreover, if a product had not been attributed all indications, this might support the perception that the biosimilar is not really similar but of lower quality than the originator product, which certainly would impact their acceptance among medical doctors and patients negatively.

3.2 Guidance in the EU and beyond

As outlined before, an adequately tailored legal and regulatory framework for the follow-up copies of biotechnology derived products was not in place when the expiration of the patent and data and marketing exclusivity provisions for the first recombinant drugs became foreseeable. Therefore the question how to best license copy biological products led to an intensive debate amongst stakeholders, mainly manufacturers and regulators, from the late 1980s on. Soon there was a consent that the established regulatory pathways for generic small-molecules would not be applicable in this case due to the complex nature of biologicals. Nevertheless, the key question remained: How and to what extent should the regulatory approval of generic followers of biologicals be allowed to rely on data and knowledge gained from the respective originator products. Based on the experience with original biologicals, an understanding evolved that extensive head-to-head product characterization and an abridged non-clinical and clinical data package should be reasonable. A reduced clinical study program for copy versions of biologicals was regarded to be necessary to demonstrate their safety and efficacy, despite the enormous improvements in analytical technologies that had occurred since the approval of the first original recombinant drugs. The physicochemical and functional characterization of a biological was not expected to sufficiently predict its biological and clinical performance, especially when considering potential side effects, such as those caused by immunogenicity, for example. [Knezevic 2011].

The legal requirements for the approval of biosimilars were first established within the European Union. The regulatory framework put into place in the EU is internationally renowned and globally paved the way for legal and regulatory provisions together with the respective WHO guideline. Australian's Therapeutic Goods Administration (TGA) for instance has adopted the European guidance completely [TGA home]. Based on the EU and the WHO guidance, the global landscape of regulations governing the licensure of biosimilars has remarkably evolved durging the last decade.

How this evolution happened over time is shown is shown in table 2 (p. 20).

As of today, the map of the world has only few white spaces left with regard to biosimilar regulations, as an impressive image (*link to image*) published in a recent review on the topic illustrates [Olech 2016]. A compilation of relevant text passages from guideline from key countries is provided in Annex II.

Because of the basic importance of the EMA's regulatory guidance on biosimilars for the rest of the world, chapter 3.2 focuses primarily on the development and the latest revisions of the respective guidelines in Euope, with a special emphasis on extrapolation.

Global evolution of guideline for Biosimilars

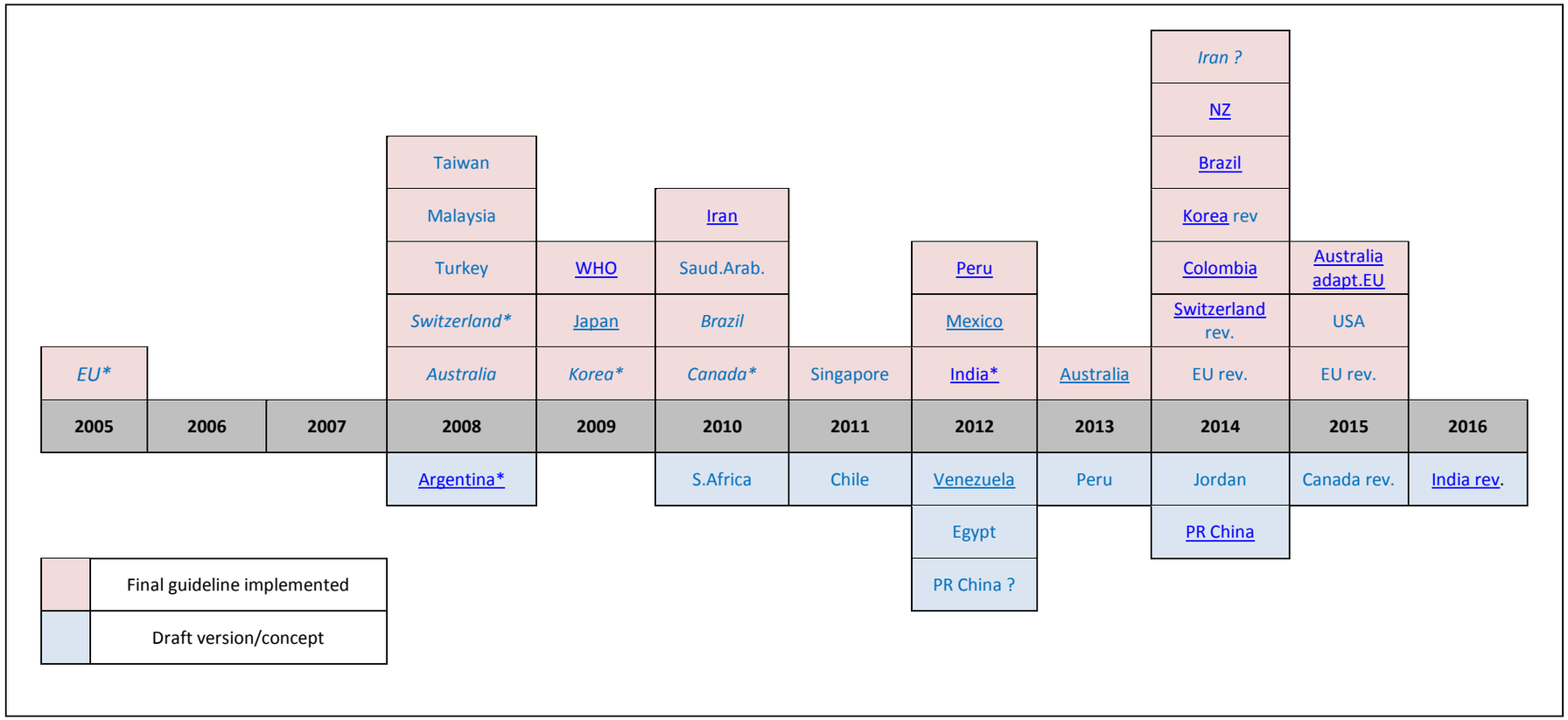


Table 2: Adopted (updated) from Krishnan, 2015

3.2.1 Europe

The European lead over other regulators in the world stems from a specific temporal coincidence: In the early 1990s, when the discussion mentioned above was in full swing, a unified European legislation on drug approval was just being constructed. Thus, in the course of laying down Community procedures for the authorization and supervision of medicinal products the involved parties paid special attention to evolving challenges. Two years before the European Medical Agency (EMA) was founded, Regulation EC/2309/93 [EC/2309/93] already determined „that it is necessary to establish a centralized Community authorization procedure for technologically advanced medicinal products, in particular those derived from biotechnology" and required that „ a single scientific evaluation of the highest possible standard of the quality, safety or efficacy of technologically advanced medicinal products, to be undertaken within the European Agency for the Evaluation of Medicinal Products" should precede the granting of such marketing authorizations. Hence, from the date of its foundation on, EMA became sort of an excellence center and knowledge hub in the regulatory evaluation of biologicals and consequently their generic successors.

In implementing the general provisions of Regulation EC/2309/93, the Community code relating to medicinal products for human use a decade later was amended by Directive 2004/27/EC. It introduced article 10(4), which clearly distinguishes the copy version of a biological medicinal product from a small-molecule generic drug by stating that the former is only similar to but not identical with its originator. It therefore stipulates the need for supplementary data in accordance with Annex I; Part II of the Community code. Its detailed provisions on specific marketing authorization dossiers and requirements lay down the legal basis for the EMA to publish scientific guidelines detailing the general principles to be applied, taking into account the characteristics of the concerned biological medicinal product. Furthermore, article 10(4) explicitly mentions "in case the originally authorized medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications" [2001/83/EC]. Thereby, the European legislation also distinguishes between generics and biosimilars with regard to granting claimed indications. In this respect, it raises the bar for biosimilars. It does not, however, generally exclude an extrapolation of available therapeutic evidence to all indications of a biosimilar's originator product, as it states that a separate "justification" may be sufficient instead of a "demonstration", which is normally expected to be given by a confirmatory clinical trial.

In fulfillment of the aforementioned legal requirements, the EMA consequently established a regulatory framework concerning similar biological products and thus already in 2005 became the first regulatory authority approaching the issue. The principles laid down by the EMA since then have been acknowledged as blueprints for their regulatory guidance in this field more or less comprehensively by other countries, e.g. Japan, Turkey, Malaysia, Australia most recently

the US and notably also India. The European approval procedure for biosimilars is generally based on a case-by-case decision. Thus, guidelines referring to specific therapeutic classes supplement three "overarching" guidelines, in which the EMA describes the basic principles of biosimilar approval [EMA home – guidance biosimilars].

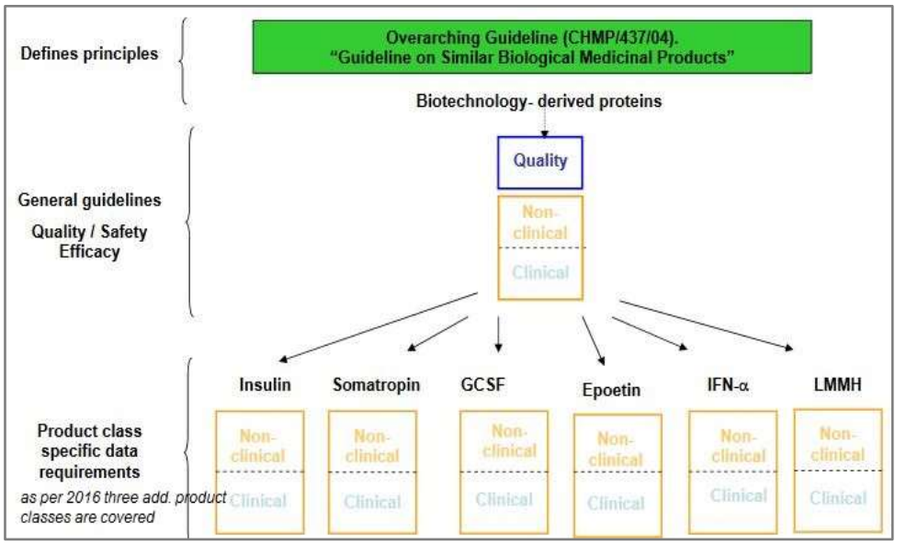


Figure 4 Framework of EU biosimilar guidelines [Ehmann 2011]

The overarching guideline on **similar biological medicinal products**, which came into effect in October 2005 [EMA/CHMP/437/04 & rev.1], introduces the biosimilar concept, defines the range of products falling under the scope of this concept, outlines the basic principles and provides reference to additional relevant guidance and provisions, which must be taken into account in order to substantiate the claim of biosimilarity.

General **quality** aspects related to the demonstration of biosimilarity are dealt with in a second overarching guideline, effective since June 2006, and already revised for the first time in 2014 [EMA/CHMP/BWP/49348/2005]. In the context of extrapolation of indications this guideline is not of interest, however.

The third overarching guideline describes the required **non-clinical and clinical** assessments [EMEA/CHMP/BMWP/42832/2005]. It provides an overview on the complete developmental study program and demands that the design of the program shall take into account all indications to be possibly claimed right from the start. It outlines the general requirements to be met regarding the choice of assays, the extent of in-vivo evaluations, and the design and scope of clinical trials, and also the topics, on which elaborated justification is expected. In this regard, special emphasis is put on the clinical safety program, including the evaluation of immunogenicity and requirements resulting thereof for risk management and pharmacovigilance management systems to be presented by the applicant.

In "certain cases", clinical comparability may be established by PK/PD studies only, without having conducted the clinical comparability study in at least one sensitive indication, which normally is requested. The special requirements, which must be met in those exceptional cases have been amended with the guideline revision in 2015 (see chapter 3.2.1.1).

The overarching guideline on non-clinical/clinical issues endorses the concept of extrapolation of therapeutic similarity demonstrated in one of the originators indications to other indications. Nevertheless, it restricts this possibility to scientifically justified "certain cases". The justification shall rely on knowledge gained from "clinical experience, available literature data, whether or not the same mechanisms of action or the same receptor(s) are involved" for every single claimed indication. Literally adopted from article 10(4) is the further provision that the particularities of each claimed indication shall be scrutinized and justified separately, irrespective whether based on the results of one confirmatory clinical comparison or deduced from the evidence of proven biosimilarity.

Interestingly, some biosimilars to Filgrastim (G-CSF biological) have been granted by the EMA all indications of the reference product based on clinical comparability proven by PK/PD studies only [Huneycutt 2015]. Regarding Filgrastim biosimilars, the applicants were given more standardized guidance through product-specific guidance, which includes determining in detail PK parameters to be regarded, the relevant clinical model and the safety follow-up period.

Providing adequate scientific advice in the development of medicinal products is one of the principles of EMA's approach. Thus, the invitation that the applicants should discuss and reconcile their development plans and objectives with the Agency is prominently laid down in the guidelines referring to biosimilars, further supporting the solicited case-by-case approach. Consequently, experiences gained and general scientific considerations are summarized in the product specific guidelines in order to provide applicants standardized, tailored requirements. As of today, nine product classes are covered by these specific guidelines. Typically, a product specific guideline describes - if deemed necessary very detailed - the design of the complete study program. It may closely describe the course how the step-wise approach should be followed. Specific assays and models to be used may be stipulated as well as parameters, markers, evaluation times and study ranges and durations. Notwithstanding that tailored safety evaluations are always product related, provisions in relation to pharmacovigilance are very detailed and may go beyond the requirements in relation of usual safety studies and post-authority measures. It may be required to take care of product specific patterns of adverse reactions, such as immunogenicity, of particularities concerning signal detection, of a structured follow-up monitoring as in registries and databases, or of risk minimization activities, to mention only a few important possible requirements.

The **class-specific biosimilar guidelines** address the issue of extrapolation in different detail, which reflects EMA's increasing experience since 2006, when it began to pioneer the assessment

and approval of biosimilar medicinal products (see Annex I). Most of the product related guidelines do only detail that indication or clinical model, which is considered being the most sensitive one and therefore qualifies for the proof of therapeutic equivalence sufficient for extrapolation of indications. These product-specific guidelines relate to [EMA home – guidance biosimilars:

- **Somatropin** (annexed to overarching non-clinical/clinical GL 2006) [EMEA/CHMP/BMWP/94528/2005],
- recombinant human **Granulocyte-colony stimulating factor** (rG-CSF, annexed 2006, under revision, concept paper 2015) [EMEA/CHMP/BMWP/31329/2005 **&** EMA/CHMP/BMWP/214262/2015],
- recombinant **Erythropoietin** (annexed 2006[1]*, revised 2010) with the additional explanation that the "mechanism of action of epoetin is the same for all currently approved indications and there is only one known epoetin receptor" and with the limitation to the same route of application [EMEA/CHMP/945626/2005 **&** EMEA/CHMP/BMWP/301636/08],
- **Interferon alpha** (2009, under revision, draft concept paper2016) with the additional note that "mechanism of action and/or the receptor are known to be the same" and if not, adequate justification should be provided [EMEA/CHMP/BMWP/102046/2006 **&** EMA/CHMP/BMWP/693108/2015],
- **Low-molecular-weight Heparin** (LMWH, 2009, under revision, draft 2013) [EMEA/CHMP/BMWP/118264/2007 **&** rev.1],
- recombinant human **Follicle-stimulating hormone** (rh FSH, 2013) [CHMP/BMWP/671292/2010],
- **Interferon beta** (2013) with the additional note that the "totality of evidence provided from the comparability exercise" will be the basis of decision [CHMP/BMWP/652000/20100].

mAbs (2012) [EMA/CHMP/BMWP/403543/2010] as the most complex product class are regulated in more detail with regard to possible extrapolation. Basically, the paradigm that the decision should be "based on the overall evidence of comparability provided from the comparability exercise" supported by adequate justification is emphasized. Comparability is expected to be shown in adequately designed PD studies. If they fail to convince, a comparative clinical trial is requested. It is underlined, however, that the biosimilarity exercise aims to demonstrate similar efficacy and safety compared to the reference product and needs not attest a therapeutic benefit – which has already been established by the reference drug. Thus, the use of clinically relevant surrogate efficacy markers in the most sensitive population – which means only in one indication – is recommended for the detection of possible product-related differences.

Nevertheless, if different indications are related to different modes of actions or or the mode of action of the originator in the respective indication is uncertain, EMA requires additional data that support comparability and a subsequent extrapolation to every single claimed indication to be presented. Each indication-specific justification should provide an extensive discussion based on state-of-the-art knowledge from scientific literature, not least covering insight concerning

[1] currently not available at EMA homepage, therefore information is taken from rev.1 (2010

mode of action, signaling pathways and the target antigen receptor(s) in question. Attention is further payed to the fact that mAb originators are often approved not only in several indications – say in different immune-mediated inflammatory diseases – but also in more than one therapeutic area, for example in cancer and immunologic diseases. In these cases, EMA requests an extensive amount of supporting data to allow for extrapolation, especially with regard to immunogenicity related safety data.

After a lengthy and very comprehensive consultation process the revision of the product guideline for **recombinant Insulins and Insulin analogues** has come into effect just recently (2015) [EMEA/CHMP/BMWP/32775/2005, rev.1]. It defines product specific requirements for granting extrapolation to other indications and also to further patient populations and the i.v. administration as well. A confirmatory clinical trial is not necessarily required. It is said that evidence of biosimilarity could only be "based on the physicochemical and functional characterization, the pharmacokinetic and, where needed, pharmacodynamic profiles".

Reviewing the content of all product-specific biosimilar guidelines with respect to their provisions on the extrapolation of indications reveals that EMA's attitude towards this issue has developed positively over time. Respective changes in these guidelines apparently reflect the agency's cumulated experience in its scientific advice on and assessment of biosimilar medicinal products und biologicals and express an increased confidence in the biosimilar comparability exercise. This confidence also characterizes the recently revised versions of the three overarching biosimilar guidelines, in which the EMA explicitly points out that the basis of its decision on an extrapolation of indications will be the "totality of evidence provided from the comparability exercise". The paradigm constituting this benchmark is that therapeutic efficacy and safety need not to be demonstrated anew because they already have been acknowledged and approved for the original reference product. This paradigm is fixed in the 2015 revision of the overarching guideline non-clinical/clinical (see 3.2.1.1). Much like in the product-specific mAb biosimilar guideline from 2012 this shows that European regulators prioritize, if any possible, suitable PK/PD-studies rather than clinical studies when it comes to establish a similar safety and efficacy. For recombinant biological drugs, which are highly purified and well to characterize, such studies are easier to conduct than for those biologicals, which are extracted from biological sources.

Very recently, the EMA has started the revision process of two of its earliest product-specific biosimilar guidelines, namely those for concerning recombinant interferon alpha and for recombinant G-CSF. In the related (draft) concept papers, nearly identical recommendations are given, even if the EMA has collected profound experience with G-CSF but not with Interferon alpha biosimilars (8 biosimilar filgrastim products have been approved so far but none from the

class of interferon alpha). More specifically, the concept paper proposes to include PEGylated substances, and to include a risk-based approach in the therapeutic comparability evaluation, as "in vitro studies .. are usually more specific and sensitive to detect differences … as in vivo-studies".

In summary, with regard to the extrapolation of indications in biosimilars EMA is obviously heading towards a new standard in the approval of biosimilars: to waive pivotal clinical comparative studies and to prefer whenever indicated a confirmation of therapeutic comparability by nonclinical in-vivo studies, using state-of-the art characterization methods and clinical relevant PD parameter. If this standard was applied to all indications of the reference product, biosimilars would predominantly come to the market without having been studied in any pivotal clinical trial. It has to be seen, whether and how stakeholders will comment on this in the ongoing (or just finished) consultation periods. Having in mind the debate, which still accompanies the extrapolation of indications from the Infliximab originator to its biosimilars (see chapter 4), the reaction is especially interesting concerning Interferon-alpha. Here, some originator drugs are also licensed for a bundle of indications, covering the treatment of cancers as well as of hepatitis, with different dose and treatment regimens. Moreover, according to the Concept paper Interferon "may have several pharmacodynamic effects. The relative importance of these effects in the different therapeutic indications is unknown".

3.2.1.1 Recent revision of the guidelines

As mentioned before, the European regulatory framework regarding biosimilar products recently underwent massive update: revisions of the overarching guidelines on Similar biological products [CHMP/437/04 rev.1] and on Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues [EMEA/CHMP/BMWP/42832/2005 rev.1] were put into force on 30 April 2015 and 1 July 2015, respectively. The revisions were undertaken based on the principle of regularly review of current guidance in order to implement insights from scientific and technological progress and from experience gained. Specifically, the growing complexity of products claiming biosimiliarity had to be addressed, as well as comprehensible demands from applicants. In particular, the tremendously improved sensitivity of analytical technology, today allows for a much more detailed characterization of the biological substance than ten years ago. It enables the detection of only minor differences, and thereby raises the bar for the proof of similarity. This needs to impact the requirements postulated in the biosimilarity exercise.

The most important amendments of both overarching guidelines are as follows:

Guideline on similar biological medicinal products

Perhaps in light of the upcoming biosimilar legislation in the US, it is emphasized that EMA's legal mandate to evaluate biosimilars for approval purposes does neither embrace any recommendation on **interchangeability** nor on substitution.

Of course does the acknowledgement of similar therapeutic efficacy mean that patients have a similar benefit when using the biosimilar, but provisions concerning substitution have to be (and are) enforced on a national level in Europe and prescribing is under the responsibilities of physicians.

The previous guidance missed a **definition** of what a biosimilar medicinal product is. In the light of various terminologies (see table) and in order to precisely differentiate from not properly regulated copies of biological drugs, the term "biosimilar" is introduced and replaces the formerly used term "similar biological medicinal product".

EMA **Biosimilar** *previously: similar biological medicinal product*	A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established
USA **Biosimilar** *previously: follow-on protein products*	[3] A biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components and demonstrates no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product
WHO **Similar biotherapeutic products** (SBPs)	Biotherapeutic product that is similar in quality, safety, and efficacy to an already licensed reference biotherapeutic product
Health Canada **Subsequent Entry Biologics** (SEBs)	A biologic drug that enters the market subsequent to a version previously authorized in Canada with demonstrated similarity to the reference biologic drug

Table 3: Terminology of biosimilars

The past experience showed a need for further **clarification,** what the **biosimilar approach** actually stands for. Therefore EMA added that

- the scientific principle of the biosimilar exercise is the same as applied in the evaluation of a possible impact caused by a manufacturing change,
- biosimilarity is not needed to be established again once the biosimolar has gained approval, not even if the manufacturing process changes,
- the posology and the route of administration must not differ from the reference product, whereas strengths, formulation, pharmaceutical form, or presentation may now differ, if adequately justified,

- improvements to efficacy do not fall under the biosimilar approach and would qualify for a stand-alone application, whereas an improved safety profile is acceptable,
- the concept of **extrapolation** is introduced at this general overarching level of guidance, saying: "if biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification". Thus, the EMA acknowledges that all indications can principally – but not automatically – be claimed for in the authorization of a biosimilar.

In order to facilitate the conduct of global development programs, now a **reference product** from outside the EU may be used in certain clinical and non-clinical in vivo studies, provided the reference product is authorized in an ICH country under comparable provisions. However, "bridging" between the biosimilar under approval, the European and the non-European reference product should include structural and functional analytics and the sponsor needs to prove the comparability between both reference products. This shift promotes not only global development, but it also avoids unnecessary clinical trials and supports a more efficient use of resources in drug development. In addition, the EMA thus contributes to harmonization of guidelines. As other regulatory authorities are already open for non-national reference biologicals (WHO, Korea, Canada, US) [Wang 2012], EMA has removed the hurdle of sticking to only locally authorized reference products.

The revision also thoroughly updates the **principles of establishing biosimilarity.** The stepwise approach to be followed is now lifted from the product-specific to the overarching level of guidance. The objective of clinical trials is determined to address potential molecular differences in order to exclude their clinical relevance. By establishing clinical equivalence in sufficiently sensitive study designs, therefore both clinical endpoints and patient populations may differ from those, which would have been required to confirm a therapeutic benefit.

In cases, where the physicochemical characteristics of the biological substance are well known, and all required characterization specifications determining biosimilarity are met, the EMA sees no longer a necessity to ask for a confirmatory trial, if not the impurity profile of the substance itself raises concerns. Experiences with some European biosimilar Filgrastims as well as US experience with Insulin and LWMH, which are approved as generics, support this thinking.

<u>Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues</u>

In general, the revision describes in much more detail the requirements to the nature and scope of the non-clinical and clinical study program compared to the preceding version. It outlines for example a roadmap to the **stepwise approach** to establish biosimilarity.

The orientation towards a **risk-based approach** concerning the non-clinical study program marks a paradigm shift in regulatory thinking, as consequently no in vivo-animal study would need to be conducted prior to a first-in man application. The need for non-clinical studies shall clearly depend on the level of concern about possibly relevant differences in quality attributes,

formulation, container closure system etc. This risk assessment requires a well chararacterized biosimilar and a profound knowledge of the specific pharmacological and toxicological properties of the reference medicinal product.

This risk-based approach reflects very well the current scientific knowledge and matches the demands of the 3Rs-initiative (**R**eplacement, **R**efinement, **R**eduction of animal models). It also addresses the fact that relevant animal models are often not available [van Aerts 2014]. Paramount to this approach is the confidence in the results and experience gained by the originator and the firm conviction that a highly similar substance will not evoke deviating reactions.

EMA 's pioneering role in introducing the risk-based approach to biosimilar development, may however currently hinder a global development, as preceding studies in animal models are mandatorily required in other legislations (US, Japan, WHO). Interestingly a recent evaluation done by Pfizer (4 mAb products, 5 studies) showed no additional insight derived from any of the required non-clinical in vivo studies [Leach 2016].

As already outlined before, the prior guidance already supported to skip a comparative clinical efficacy study in "certain cases" if guideline requirements were met. The revised requirements are more precise, but have not changed principally, even if the importance of specified surrogate PD markers is now emphasized, which are capable to indicate and quantify effects that are relevant for the clinical outcome, for example early viral load reduction of interferon alpha in hepatitis C. Alternatively, non-surrogate PD markers may be used, which do not indicate efficacy directly but rather the pharmacological action. They have to show a clear response/dose relationship at several drug levels (in the steep part of the response curve). Only in exceptional cases – as before - a combination of well characterized PK patterns is acceptable, with various non-surrogate PD markers ("fingerprinting") tested with different drug concentrations.

Regarding clinical efficacy studies the guideline introduces **comparability margins** empowered to establish equivalence. Nevertheless, EMA assessors stated that a non-inferior design may also be accepted in order to keep studies feasible and not require large studies as has they had to be conducted in the registration of the originator biological [EMA workshop 2013, panel].

Safety requirements are not changing, but are described in more detail, i.e. in relation to the design and duration of studies. Basically, comparative safety data should be collected and a safety profile is to be established for each indication separately. The revision makes reference to a separate guidance dealing in particular with immunogenicity assessment. This guidance is meanwhile in place and points out that differences in the immunogenicity profile will put biosimilarity into question at all.

With regard to the **extrapolation of indications** the revision makes the guideline less restrictive and provides in parallel more detailed reasonable requirements. Instead of accepting extrapolation only in "certain cases" the concept now always "could be acceptable, but needs to be scientifically justified". The revised guideline states that "it is expected that the safety and efficacy can be extrapolated when biosimilarity has been demonstrated". It expresses explicitly that justification shall normally rely on the outcome of physicochemical and structural analyses, in-vitro and in-vivo (functional assays) and human PK/PD data in one indication – which means that the usual armamentarium for establishing comparability is expected. It does not mandatorily call for a complementary clinical trial to establish efficacy and safety. It does acknowledge, however, that immunogenicity may differ between indications because it depends also on factors beyond the analyzed physicochemical substance characteristics, which at this stage of the development have been proven to be similar. Therefore, it points out that immunogenicity must be assessed separately to be allowed to extrapolate from one indication or a particular route of administration to another one. It endorses that safety issues, which may occur in different subpopulations – and hence in patients suffering from different diseases – have to be already addressed when setting up the non-clinical safety program.

The revised guideline clearly defines the basis for every sound scientific justification of extrapolation: The mechanistic understanding of both the pathogenesis of each concerned indication and all potential interferences of the biosimilar therewith. Applicants and regulators shall in this respect rely on data deriving from former research with the reference product and on currently evolving scientific knowledge. Basically, receptors are in the focus of this quest: Does the active biological substance molecule inherit different active sites, which may act differently in various diseases and population? Are the same receptors involved in different indications/populations? Is the receptor distribution and concentration similar in various indications/populations? Does the susceptibility of signaling pathways vary with different receptor locations and diseases?

The revised guideline also underscores that only studies in a sensitive population will qualify for the extension to other indications, saying that additional data will be requested if "the studied therapeutic indication is not relevant for others in terms of efficacy or safety, i.e. is not sensitive for differences in all relevant aspects for safety and efficacy".

All in all, in order to address the underlying particularities for the additional indications in question, the putative biosimilar must prove its established physicochemical comparability only in additional functional assays, which are meaningfully chosen with regard to the additional data requirements and sensitive enough to detect potential differences. The aim is to demonstrate that no differences exist and not to show effects of whatever extent.

Thus, the challenge of extrapolation is to find out which data must be generated to detect differences in disease pathogenesis, in therapeutic mode of actions and in possible population derived parameters such as influences coming from co-medications or typical concomitant diseases.

The important thing in proving similar efficacy and safety is showing absence **-** absence of differences between originator and biosimilar, which is due to their higher sensitivity preferably requested to be shown in non-clinical, tailored functional assays. EMA regulators rely on this proof of similar efficacy and safety, if an appropriate scientific explanation is given, and are prepared to waive, to mention it again, comparative clinical trials, which are usually not adequately powered to detect differences.

The overarching biosimilar guideline clinical and non-clinical issues does not explicitly address, whether differences related to different age groups or routes of administration may require on extrapolation approach as well. If deemed necessary, such provisions are included in single product specific biosimilar guidelines, e.g. for epoietin and insulin. Nevertheless, it will be in the distinction of the applicant to discuss the relevance and appropriate action(s) with the EMA, asking for scientific advice.

A comprehensive explanation of the EMA's view of extrapolation issues at the time of the revision of the overarching guidelines for biosimilars is provided in the publication "Biosimilars. The science of extrapolation" [Weise 2014].

3.2.2 World Health Organization

From the first, WHO played an active role in the harmonization and worldwide application of the guidelines and scientifically based principles for the licensure of biosimilars. A WHO working group took the helmet in 2007 and started the development of a consensus guidance in the regulation of biosimilars. One has to keep in mind that at that time the discussion whether and how an approval package for a copycat biological should be differentiated from a generic application dossier was still ongoing. Substantial disagreements between different regulatory bodies regarding scope and content of the non-clinical and clinical evaluations to be provided were apparent. Moreover, it was obvious at that time that in some regions of the world copycat biologicals were already marketed, which had been approved on the basis of reduced data packages that probably did not always comply with high regulatory standards. [Joung 2008, Knezevic 2011]

In 2009 the "Guidelines on evaluation of similar biotherapeutic products" were published, aiming to contribute to the availability of save and effective biosimilars worldwide [WHO 2009]. This was an important step forward in establishing the "biosimilarity" approach, which relies on the demonstration of essential similarity in a head-to-head comparison of the originator product and the biosimilar that requests registration. [Knezevic 2011].

Remarkably, with regard to the extrapolation of efficacy data to other indications held by the reference product, the WHO guideline goes into more detail than the EMA guidance, which was in place at that time. The WHO guideline proposes to use an equivalence rather than a non-inferiority design when establishing similar efficacy, as this would facilitate extrapolation; this aspect has been introduced in the latest revision of the EMA's non-clinical/clinical biosimilar guidance, too.

Nevertheless, the main conditions to be met by a biosimilar all together are comparable, even if EMA explicitly asks for a separate justification in each involved indication. Generally, the indications should share an identical mode of action and/or the same target receptors. If not, sound scientific justification is required. WHO literally demands additional data and thereby already introduces the concept of a possibly supportive "PD-fingerprint" (roughly: combination of a bundle of PK studies and PD-biomarker studies) instead of further clinical studies. Safety concerns should have been excluded for further indications. In this respect, the WHO guideline provides examples referring to critical sub-population issues and specifically mentions that immunogenicity matters. It points out as well that a clinical test model must be chosen, which is able to detect potential differences between the putative biosimilar and the reference product.

All in all, the WHO guideline is in line with the then evolving consensus of regulators on the requirements for extrapolation of indications.

WHO currently continues its active role in contributing to the evaluation, dissemination and implementation of regulatory standards in general and in particular concerning the development of biosimilars. It collaborates closely with the dedicated working group at IPRF (International Pharmaceutical Regulators Forum) [WHO 2016]. In acknowledgement of the importance of extrapolation issues, a joint Reflection Paper for extrapolation of indications is under development [IPRF 2015]. This reflection paper will recommend how a biosimilar can demonstrate to have the same mode of action and the same target receptor as its reference product; what models are most sensitive for clinical studies, differentiated by product class; how to conclude extrapolation of indications from the totality of evidence; and the role of quality assessment and nonclinical data in providing assurance for extrapolation. According to the chair of the respective working group, the Reflection paper is planned to be published on IPRF's website in Q3/2016 [Park-Y 2016]. It can be speculated that this Reflection paper may in the long run end up in a revision of the current WHO guidelines, but certainly its results will contribute to the educational efforts the WHO is undertaking to support the implementation of current science-based principles namely in developing and BRIC countries.

Another joint WHO/IPRF biosimilar project came up with a template for Public Summary Information for Biosimilars (PASIB), which aims to enhance transparency and to facilitate knowledge transfer between regulatory bodies [IPRF home].

3.2.3 Comparison of extrapolation requirements

Clearly, the pioneering EMA biosimilar guidelines and those of the WHO, which have contributed to global harmonization, have most decisively framed the regulatory assessment of biosimilarity worldwide. Other and subsequently released country specific guidance documents are strongly orientated towards them.

The legal basis for the development and approval of biosimilars in South Korea was established in 2009. In the same year the related guidance was enforced. It has been revised in 2014. The amendments do not touch extrapolation requirements [Joung 2015, Park 2016]. Although the Korean guidelines are widely appraised to follow the WHO framework, they have been supplemented by various product-class specific provisions recently.

In Canada, a first guidance came into effect in 2010. For the purpose of revision, it is currently being discussed in a consultation phase. According to the self-assessment of representatives from Health Canada "EMA's position on the extrapolation of indications is similar to that of BGTD's (Biologics and Genetics Therapies Directorate at Health Canada]; the approval of indications would be based on the evidence in the submission package, and all indications would not be automatically applied on the basis of a single bio-equivalence study" [HC 2011]. There is no evidence that this self-assessment has changed – despite Health Canada's divergent decision concerning the extrapolation of all indications of the infliximab originator to its biosimilar (see chapter 4).

Obviously, different decisions of regulatory authorities are not necessarily deducable from different provisions written down in their guidelines, but more so from their interpretation of these guidelines on a case-by-case basis, founded on the ground of best avaible knowledge. All regulators explicitly take a careful approach in deciding on extrapolation of indications and in that are primarily orientated towards the well-being of patients.

The legal basis for registration of biosimilars in the US was laid down in 2009 with the Affordable Care Act, which includes the Biologics Price Competition and Innovation (BPCI) Act. Subsequently, a first FDA draft guidance was published in 2012 [FDA home – Guidance biosimilars]. It came into effect in 2015 and contains requirements to be met for extrapolation of indications. A more detailed definition of the quality and scope of clinical pharmacological data, which are necessary to justify an extrapolation of indications was only drafted in 2014. Interestingly the BPCI Act states that a biosimilar "is expected to produce the same clinical results in any given patient," and concludes that under this condition "the biologic product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product." Therefore, stricter rules are eagerly expected to follow. Most reasonably, they may encompass positive results from switching studies, that will qualify for this "automatic" interchangeability.

As currently another master thesis examins the entrance of the first biosimilar(s) into the US market, more US specifics will not be disussed in this thesis.

As has been shown by the previous presentation of the EMA and the WHO guidance, the principle requirements of both are similar and are evolving towards clearer and more specific definitions. Both guidances have influenced each other in close interdependence.

Nevertheless, certain differences and distinctions concerning the extrapolation of data when applying for the indications of a reference drug, still exist, as the following table shows in very condensed form.

Issue	FDA	EMA	Canada	WHO	Korea	Japan
		Biosimilars	Recombinant protein protein drugs			Recombinant proteins and polypeptids
Mechanism of action may be distinct in each therapeutic indication /	Extrapolation will be considered on a case-by-case basis. Where the mechanism of action differs between indications or are not fully understood, Totality of data / evidence to be regarded		Issues related to MoA should be discussed on a case by case basis with HC	The clinically relevant mechanisms of action and/or the involved receptors should be the same for the different indications , otherwise strong sci. rationale and add data		Where each relevant indication have a different mechanism or the mechanism is not completely known, extrapolation is not applicable, efficacy with RP to be demonstrated for each indication
Add. data required	s. above	depending on spec. case, preferably specific functions assays ,	s. above	PD fingerprint, clinical trials	n.a.	n.a.
Safety profiles in different patient groups	Data should be produced using a patient population and clinical end point most sensitive to detect clinically meaningful differences in efficacy and safety		Characteristic of different patient populations, influence of concomitant therapies/ conditions should, risk and impact of immunogenicity are adequately to be considered throughout the whole comparability development program Seek advice	A sensitive clinical test model should be used that is able to detect potential differences between the follow-on and reference products.		n.a.
Individual patient characteristics may influence the response	Careful consideration must be given to comorbidities/concomitant medications and intersubject variability	Homogenous population should be used-differences in response can then be attributed to the biosimilar		The safety and immunogenicity profiles of the follow-on products should be sufficiently characterized.		n.a.

Table 4: Comparisíon of extrapolation requirements (extensifely modiefed from Park-D.I. 2016)

The most crucial prerequisite, commonly requested by all regulations is that the reference product and the biosimilar under registration share the same targets and mode of actions throughout all indications, licensure is applied for.

Overall, it has be acknowledged that globally EMA and FDA require the most comprehensive structural and functional comparative data, before they allow to initiate animal and human studies. Whenever scientifically justified, EMA already skips animal studies in most cases. This also concerns the establishment of evidence for the extrapolation of indications. Presumably, this will soon also be reflected in the FDA guidance. In general, the global alignment of

standards for the registration of biosimilars including the extrapolation issue will most probably steadily grow, as regulators more and more interact internationally.

4. The special case of Infliximab

Infliximab is a chimeric monoclonal antibody (mAB), manufactured from a recombinant cell line. It binds both to soluble and transmembrane forms of tumor necrosis factor alpha (TNF-α), a key mediator of cell proliferation in inflammation, and thereby inhibits inflammatory processes. It also activates immune responses, triggering for example antibody-dependent cell-mediated cytotoxicity.

Infliximab contains approximately 30% murine components, which confer the antigen-binding specificity to human TNF-α. The remaining 70% correspond to a human IgG1 heavy chain constant region and a human kappa light chain constant region. [EMEA Remicade EPAR 2005] Like all antibodies, Infliximab is a highly complex, globular and multiply folded glycoprotein. It has a molecular weight of 144,2 Kilodalton and consists of 1328 amino acids (450 in each heavy chain and 214 in each light chain), which undergo many post-translational modifications through glycosylation and carbohydrate attachment. [Dörner 2015]

Under the brand name Remicade, Infliximab was first approved by the FDA for the treatment of Crohn's disease in August 1998, and subsequently for the treatment of rheumatoid arthritis in November 1999. In the EU, Remicade received its first approval for the treatment of rheumatoid arthritis, in combination with methotrexate, in August 1999. As of today, Infliximab is approved for six indications both in Europe and in the US and many other countries of the world, namely:

- Crohn's disease (CD[2]) including pediatric CD,
- Ulcerative colitis (UC) including pediatric UC
- Rheumatoid arthritis (RA)
- Psoriatic arthritis (Ps)
- Ankylosing spondylitis (AS)
- Plaque psoriasis$\alpha\alpha$

Remicade was the first approved anti-TNF-alpha agent and hence the first targeted biologic therapy, thus being kind of a medical revolution. It did not only improve significantly the disease status of patients, which suffer from such a chronically debilitating disease as RA. It helped also to treat or even cure other inflammatory diseases, which had been regarded as quite different from RA before. Not surprisingly, other medicinal products also targeting the TNF-α inhibitors were developed and launched successfully, namely the two fully human mABs Adalimumab

[2] In scientific papers and regulatory documents, CD and UC are often summarized under the acronym IBD, which stands for inflammatory bowel disease

(Humira) and Golimumab (Simponi), the fusion protein Etanercept (Enbrel), and the PEGylated Fab fragment Certulizumab pegol (Cimzia). Physicians realized that seemingly unrelated diseases such as RA and CD obviously shared a similar immune dysregulation. This led them to the definition of immune-mediated inflammatory diseases (IMIDs) and consequently from an organ-based to a mechanism-based treatment [Kuek 2007].

For good reasons, Remicade (like other biologics) became a big commercial success. During the last decade, it constantly ranked among the best selling pharmaceutical products of the world. In 2014, its global sales amounted to 7.9 billion US-Dollars. In February 2015, however, its patent expired in the EU. In the US it will expire in September 2018. Manufacturers of biosimilars had long prepared for these dates [Long 2015].

The South Korean biotechnology company Celltrion developed the first infliximab biosimilar (project name CT-P13). It was therefore no surprise that this biosimilar - under the trade name Remsima - was first approved in its home market by the Korean Food and Drug Administration (KFDA) on 23 July 2012. On 28 June 2013, this first infliximab biosimilar was approved by the EMA and received marketing authorization throughout the European Union by the European Commission on 10 September 2013. In the EU, it is marketed as Remsima by Celltrion and as Inflectra by Hospira, a subsidiary of Pfizer.

Since then, Celltrion has also gained approval for Remsima in South Korea, Colombia, Japan and Canada. Brazil also approved Remsima, as its first follow-on biological medicine, through its pathway for follow-on biological products, in April 2015. In the US, FDA has approved Inflectra on 5 April 2016.

The approval and subsequent launch of Remsima and Inflectra in the EU in February 2015 made the by far most complex molecule ever available as a biosimilar to medical practice. To underscore their huge difference from "traditional" biosimilars for agents like erythropoietin or filgrastim, antibody biosimilars in general have been dubbed Biosimilars 2.0 [Apothekerbank 2015]. The advent of the first Infliximab biosimilar as the protagonist of this class has led to controversies between regulators, clinicians (mainly learned societies) and other stakeholders (e.g. pharmaceutical companies) about the justification of extrapolation of indications for a product of this complexity and with such a broad field of therapeutic applications. These controversies will be described on the following pages.

4.1 Regulators' rationale for approval of infliximab biosimilars

In accordance with the legislation enforced in 2009 in South Korea, the approval of Remsima and Inflectra, respectively, was based on an extensive physicochemical characterization of

CT P13 in relation to the infliximab original that demonstrated the highly similar properties of the two molecules [Soon Kwan Jung 2014] and on the clinical comparison of the biosimilar to the originator molecule in three PK/PD studies: a preliminary study in 19 patients with active RA who additionally received methotrexate (MTX) for over 100 weeks; a phase I in 250 AS patients (PLANETAS) over 30 weeks; and a phase III study in 606 RA patients with concomitant MTX medication (PLANETRA) over 30 weeks.

The PLANETAS study was a multicenter, parallel-group, prospective double-blind study to mainly compare the PK profile of CT-P13 and Remicade. It showed that both compounds are bioequivalent in terms of Cmax (maximum serum concentration) and AUC (bioavailability) and also display a high similarity in several secondary PK endpoints. Additionally, both compounds were comparably well tolerated and efficacious [Daller 2015]. It is noteworthy that PLANETAS included two to ten times more patients than phase I studies for first generation biosimilars such as somatropin or filgrastim did [Huneycutt 2015]. This is in line with EMA's recommendation that small PK studies are not sufficient for biosimilar monoclonal antibodies because of the latter's large person-to-person-variation in PK parameters. In its assessment report for the approval of Inflectra the EMA also emphasized the suitability of the indication AS for drawing conclusions on the molecule's general PK profile in other potentially relevant indications: "Patients with AS were considered as a sensitive population, because these patients are generally young, otherwise healthy and not receiving concomitant medication such as MTX, which has been shown to have an effect on anti-infliximab antibody status and thus on infliximab clearance" [EMA EPAR 2013, p.59].

The PLANETRA study was designed to demonstrate equivalence in safety and efficacy between CT-P13 and Remicade. In a randomized, double-blind setting it enrolled 606 patients with active RA despite previous MTX treatment to receive either 3mg/kg CT-P13 or Remicade with MTX and folic acid. The primary endpoint was the American College of Rheumatology 20% response (ACR20) 30 weeks after the beginning of treatment. Equivalence of efficacy would be reached if the 95% confidence interval (CI) for the treatment difference was within -15% to +15%. At week 30, ACR20 responses were 60.9% for CT-P13 and 58.6% for Remicade (95% CI −6% to 10%) in the intention-to-treat population. Concerning safety, the incidence of drug-related adverse events (35.2% vs.35.9%) and the detection of antidrug antibodies (48.4% vs. 48.2%) were highly similar for CT-P13 and Remicade, respectively [Yoo 2013]. The EMA acknowledged the PLANETRA study as „adequate to support this biosimilar application" and underlined that „the choice of the indication (RA), the clinical setting (patients not adequately controlled with MTX), the primary endpoint (ACR20 at Week 30) and the equivalence margin (± 15%) are in line with the CHMP guidance and were endorsed in CHMP scientific advice" [EMA 2013, p.80].

Immunogenicity had been monitored not only in PLANETRA but in all three studies, which were submitted to gain approval, as infliximab is known to be highly immunogenic.

4.2 Extrapolation to inflammatory bowel disease (IBD)?

4.2.1 The regulators' view

„Based on the results of the extensive *in vitro* and *ex vivo* comparability data on all functionalities of the infliximab molecule, including several experiments especially relevant to IBD", EMA gave green light for the extrapolation of the pharmakokinetic, efficacy and safety results gained in with CT-P13 in the indications RA and AS to all other indications in which the originator product Remicade had been approved. The agency emphasized that its decision was „supported by increasing genetic and immunological evidence of a clinical and histological overlap between gut inflammation in spondyloarthropathies and CD" and also positively referred to „preliminary clinical data from a small cohort of South Korean patients with CD and UC", which indicated „similar response to CT-P13 compared with historical data on Remicade" [EMA 2013, p.104].

Roughly half a year later, in early 2014, the Canadian regulatory authority Health Canada evaluated the same CT-P13 data differently and decided to allow an extrapolation only to psoriatic arthritis and plaque psoriasis, but not to IBD. In its summary basis for decision it stated that "extrapolation to indications and uses pertaining to Crohn's disease and ulcerative colitis could not be recommended due to differences between Inflectra and the reference product, that could have an impact on the clinical safety and efficacy of these products in these indications." [HC SBD 2014]

Despite of these different decisions, EMA seems to share at least partly the concerns of its Canadian counterpart. In its assessment report on Inflectra it did not only recommend post-authorization monitoring of the product's safety and efficacy in general, but more specifically asked also for a PAES (post-authorisation efficacy study) in active CD versus it#s reference Remicade „provide further efficacy data in the treatment of IBD" [EMA 2013, p.104]. This randomized, double-blind, parallel-group study with 220 patients enrolled started in July 2014 and is expected to be completed by February 2017 [NCT02096861].

The FDA warranted extrapolation to all indications for which Remicade is approved and thus principally shared EMA's previous decision. The FDA based its approval on the evidence presented at the hearing of its Arthritis Advisory Committee on 9 February 2016 [FDA 2016a]. Advisers had come to the conclusion that there are no clinically meaningful differences between Inflectra and Remicade in terms of the safety, purity and potency of the product. They had voted 21 to 3 in favor of the recommendation to approve CT-P13 in all indications of the originator product [FDA 2016b].

4.2.2 The concerns of clinicans

The controversy between EMA and Health Canada is reflected in the opinions of several learned societies in Europe. While some of them are quite outspoken in their criticism of EMA's allowance for full extrapolation, others strive to formulate more balanced calls for caution. The European Crohn's and Colitis Organization ECCO, for example, published its position statement on the use of biosimilar medicines in the treatment of IBD already whilst the EMA assessment for approval was still ongoing. ECCO emphasized "that that the use of most biosimilars in patients with IBD will require testing in this particular patient population, with comparison to the appropriate innovator product". In other words: Extrapolation to IBD should not be allowed at all. In contrast, "specific evidence obtained in patients with IBD should be required to establish efficacy and safety for this specific indication, because experience with currently licensed biological medicines has already shown that clinical efficacy in IBD cannot be predicted by effectiveness in other indications, such as rheumatoid arthritis" [Danese 2013].

Similar concerns were raised by the Italian Group for Inflammatory Bowel Disease: "It is highly recommended that, when the reference drug is used to treat IBD, evidence of the biosimilar's efficacy and safety in this specific setting be obtained prior to marketing." According to the Italian group this would be all the more necessary as there are currently no specific and clear-cut biomarkers available "that can be used to predict IBD patients' responsiveness to these agents and to monitor their short-term efficacy (like hemoglobin level for epoetin therapy or glucose levels for insulin) " [Annese 2014]. The phenomenon that no direct pharmacodynamic markers exist for their activity and that clinical trials have to be designed around relatively insensitive clinical endpoints among experts is perceived as a general problem of monoclonal antibody drugs and as a challenge to study their safety and efficacy especially in oncology [Ebbers 2016].

The Spanish Societies of Gastroenterology and of Pharmacology jointly even declared: "In no case does a license obtained for the management of a certain disease allow an extrapolation of results to a different disorder. In this way, results obtained from studies in RA should not be extrapolated to IBD" [Arguelles-Arias 2013].

In Poland, a group of experts involved in various aspects of biological therapies, concluded that although biosimilars of monoclonal antibodies and fusion proteins "may be applicable in indications and/or patient populations approved for the reference drug despite the lack of formal studies, such extrapolations must be approached with caution" and that „more experience in this field is required" [Jahnz-Rozyk 2014].

4.2.3 Specific issues at stake

The debates that have been triggered by the difference between EMA and Health Canada and the arguments that are accordingly put forward by clinicians and learned societies can be

attributed to three major issues:

- mode of action
- pathophysiological differences
- sensitivity of RA as a model for IMIDs

Mode of action

A crucial prerequisite of extrapolation is that the original biological and its biosimilar share the same mode of action in all indications licensure is applied for. Health Canada doubts that this is the case for CT-P13 in IBD. It argues that the original TNF-alpha inhibitors may exert a dual mode of action in IBD, which CT-P13 possibly might not fulfill. Predominantly, infliximab (and adalimumab) target soluble TNF-alpha molecules. In patients with IBD, however, they have been shown to target the TNF-alpha receptors of immune competent cells, too. The binding to these transmembrane TNF-alpha molecules is mediated by the Fc region of the monoclonal antibody. This binding results in certain effects of antibody-dependent cellular cytotoxicity (ADCC). It is the more effective, the less fucose sugars are contained in the oligosaccharides that are attached to the Fc region during post-translational glycosylation. For this reason, therapeutic mABs are designed to be afucosylated [Tracey 2008]. CT-P13, however, has a lower level of afucosylation than Remicade. Consequently, it performed worse than Remicade in the most sensitive ADCC assay, which used natural killer cells and transmembrane TNF-expressing Jurkat cells as the effector and target cells, respectively.

As "ADCC cannot be ruled out as a mechanism of action in the inflammatory bowel diseases (IBD)", Health Canada therefore declined to approve CT-P13 for this indication by extrapolation. "This position is supported by the observation that certolizumab pegol, another anti-TNF that lacks the ability to induce ADCC, displays only marginal efficacy in Crohn's patients compared to other anti-TNFs, namely infliximab." EMA interpreted the same data rather differently. It considered the lower amount of afucosylation of CT-P13 not as clinically relevant and relied more on those ADCC assays, in which CT-P13 and Remicade displayed a similar performance and which it judged to be "most relevant to the pathophysiological conditions", e.g. assays using whole blood cells as the effector and lipopolysaccharide-stimulated monocytes as the target cells [Isaacs 2015]. Additionally, EMA pointed out that "the contribution of ADCC to the mode of action of infliximab, or any TNF antagonist, has not been established in patients and ADCC may be limited in inflammatory focus *in vivo".* [EMA 2013, p.103]. An expert from the German BfArM underlines that the biosimilar and its original both showed a similar induction of regulatory macrophages that is implicated in the mode of action of infliximab in IBD [Weise 2014].

Pathophysiological differences

Rheumatic diseases and inflammatory bowel diseases are distinguished by pathophysiological differences that relate both to the diseases themselves as to the respective patient population. These differences make "a direct extrapolation between the two groups challenging without clinical or PK/PD bridging data" [Health Canada]. With regard to pharmacokinetics, there are multiple pathways through which monoclonal antibodies are distributed, metabolized and eliminated. Infliximab exerts its actions in various tissues (joints, skeleton, gastrointestinal tract, and skin). Yet its tissue-specific concentration required for clinical effectiveness is not known. Drug levels measured in serum may only be inadequate surrogate markers for drug levels in the tissues. This would make extrapolation questionable, as it relied on the assumption that the originator product and its biosimilar achieve similar distribution to all affected tissues, the authors of an originator-sponsored review remark. They also argue that it should make regulators think that Infliximab clearance considerably varies between patients with CD and patients with RA, and that the potential effects of concomitant drugs had also to taken into account. Comparative PK data from the repeated-dose study in AS might thus not be be reflective of PK in other indications [Feagan 2014]

The challenge of different pathophysiology also involves safety aspects. Health Canada emphasizes that „the risk of hepatosplenic T-cell lymphoma appears to be uniquely associated with the inflammatory bowel diseases occurring in adolescents and young adults" [HC 2014] and that the data it had received for approval of CT-P13 had not clarified how differences between the biosimilar and its reference product may affect this risk.

Different dosing schemes of Infliximab treatment in RA and in IBD patients are debated as a potential hurdle for extrapolation, too. The main reason for the concern against an extrapolation across doses is that in the PLANETRA study a dose of 3 mg/kg was given, while the labeled dose for IBD is 5 mg/kg [Fiorino 2014, Danese 2014]. Yet this argument can be countered by the notion that the phase I PLANETAS study had established the PK equivalence of CT-P13 at a dose of 5mg/kg [Isaacs 2015]. Nevertheless, a group of Canadian regulators insists that "extrapolation could be considered inappropriate when the proposed dose and schedule differ between the studied indication(s) and the indication that has not been studied " [Scott 2015].

Looking forward to the first biosimilar of rituximab that has just entered the approval process at the EMA, the group of Canadian regulators remind us that rituximab - following clinical trials in each indication – is approved for use in patients with rheumatoid arthritis as well as for patients with non-Hodgkin's lymphoma (NHL). Extrapolation from RA to NHL, however, "would be inappropriate for several reasons. First, the diseases themselves are very different. As well, the population characteristics are quite different, especially in terms of prior therapies. Furthermore, the pharmacokinetic profiles of rituximab differ due to the target-mediated clearance exhibited by patients with large tumor burdens such as those with NHL" [Scott 2015].

Sensitivity of RA as a model for IMIDs

Patients with rheumatoid arthritis receive infliximab together with the MTX, which due to its immunosuppressant activity inhibits the formation of antigen-dependent antibodies (ADAs). In IBD patients in contrast, Infliximab normally is administered as a monotherapy. As ADAs are the mediators of immunogenicity, which may lead to reduced clinical efficacy and increased risk of adverse advents, it could well be that due to the effect of the concomitant MTX they appear to be lower in RA than they really are in monotherapies without MTX. Therefore, it had been questioned whether the immunogenicity of CT-P13 has been investigated in populations sensitive enough to justify extrapolation [Ben-Horin 2015]. The counter-argument to this concern highlights the sensitivity of the assays used for ADA detection as the critical factor for assessing immunogenicity and states that the respective assays in PLANETAS and PLANETRA were highly sensitive and both in AS and RA patients did reveal no differences between CT-P13 and Remicade [Isaacs 2015].

The sensitivity of RA models for generating clinical evidence for immune-mediated inflammatory diseases (IMIDs) in general has also been questioned on statistical grounds. It has been suggested that the difference in efficacy between a treatment and a placebo needs to be high to prove a difference between this treatment and a similar treatment in a different trial. With regard to the six approved indications of infliximab this would mean that the indication with highest placebo-adjusted response rate in its original approval trial is best suited to detect potential differences between infliximab and its biosimilar. In this respect, however, RA was associated with the smallest placebo-adjusted response to infliximab whereas the greatest responses were found in plaque psoriasis, followed by psoriatic arthritis and Crohn's disease. Thus, the extrapolation from RA and AS to all other indications in which the originator was approved would have been based on the least sensitive clinical indication [Lee 2015]. Opponents of this opinion argue that the decision to conduct the pivotal clinical trial for the approval of CT-P13 in RA was based on the fact that RA is the most common inflammatory rheumatic disease and that also the extent of clinical experience in this indication is greater than in all others in question [Isaacs 2015]. This argument is in line with EMA's statement that "this clinical model (RA) was considered sufficiently sensitive to enable the detection of differences between the two products" [EMA 2013]

4.3 Current study and approval status of infliximab biosimilars

By April 2016, the first Infliximab biosimilar had already been approved in 71 countries across the globe. In the meantime, a second infliximab biosimilar, developed by a joint venture of Samsung and Biogen called Samsung Bioepis, has been approved by the EMA on 1 April 2016 under the name Flixabi. Based on safety and efficacy data from a phase III clinical study in 584

RA patients, EMA granted extrapolation to all indications of originator infliximab. Samsung Bioepis' etanercept biosimilar Benepali had been approved by the EMA in January 2016 for the treatment of rheumatoid arthritits, psoriatic arthritis, axial spondyloarthritis and plaque psoriasis.

According to EMA's list of application for new human medicines under evaluation by the Committee for Medicinal Products for Human Use (CHMP) released on 13 April 2016, it is currently reviewing applications for the approval of four further mAB biosimilars, namely Adalimumab (2), Rituximab (1) and Etanercept (1) [Gabionline, 6 May 2016]. So one can expect that the controversies about extrapolation of indications will continue for some time, although some experts predict that "many of the concerns raised with regard to extrapolation appear to be hypothetical, and will likely not be problematic in the long term" [Dörner 2016].

An important contribution to reconcile the current controverse positions about extrapolation of indications for infliximab biosimilars could come from switching studies in real world settings. These randomized, double-blind and parallel-group studies evaluate the safety and efficacy of switching from Remicade to its biosimilar infliximab compared with continued treatment with Remicade in all approved indications. A prominent example is the NOR-Switch study, sponsored by the Norwegian state. 498 patients have been enrolled with the intention to treat them for at least 12 months.

Currently several efforts are underway to collect real-world data about transitioning. One example is the NOR-SWITCH study, supported financially by the Norwegian government. NOR-SWITCH was designed as a non- inferiority study over 12 months to evaluate maintenance of effi- cacy as well as adverse event monitoring following transitioning from reference to biosimilar infliximab, compared with main- taining treatment with the reference product in patients with RA, SpA, PsA, Ps and IBD. Eligible patients on stable treatment for at least 6months were randomised to either continue treatment with reference infliximab or to transition to CT-P13. The primary end point of this study is disease worsening. Enrolment was completed in June 2015; 498 patients were randomized. Those who complete 12 months' treatment are then asked to participate in an open-label follow-up study during which all patients will receive the biosimilar for 26 weeks. Results from this study are expected to be available at the end of 2016. Results are expected in January 2017 [NCT02148640].

In extensions of both the PLANETAS and the PLANETRA study (after the primary endpoint had been reached), the effects of switching from Remicade to CT-P13 had already been studied in AS and RA patients. In both extension studies, switching had not detrimental effect on efficacy and safety when compared with non-switched patients [Müller-Ladner 2015].

At the ECCO Conference in March 2016, data from real-world studies with nearly 600 IBD patients from eight countries were presented, which showed a comparable efficacy and safety following a switch from originator infliximab to its biosimilar [Biosimilar News March 23, 2016].

Based on positive post-marketing experience in patients with IBD, the British Society for Gastroenterology (BSG) had already recommended in February 2016 to switch the treatment of stable IBD patients from originator to biosimilar infliximab: „There is sufficient evidence to recommend that patients who are in a stable clinical response or remission on Remicade therapy can be switched to Remsima or Inflectra at the same dose and dose interval. This should be done after discussion with individual patients, with explanation of the reason for switching (which is usually on the grounds of benefit to the overall service by reduction in costs of the drug and its administration)" [BSG 2016].

5. Discussion

During the last three decades, extrapolation has emerged as an essential element of drug regulation and approval. For regulators, it is in many ways necessary to draw conclusions from a naturally limited base of data in an application file in order to make meaningful decisions. Accordingly, as described in chapter 2 of this thesis, a framework of regulatory guidance on extrapolation in general has been evolving since the 1990s. Thus, extrapolation is not a new concept. Not even extrapolation of indications for biosimilars is a new concept, although one could have this impression when following the heated debate between regulators and learned societies since the EMA has approved the first monoclonal antibody biosimilar for all indications of its originator product 2013. In fact, EMA has internationally pioneered the extrapolation of indications, as described in chapter 3 of this thesis and EMA regulators have accumulated a large body of evidence in the assessment of biosimilar applications, which justifies their confidence in extrapolation of indications.

In the case of filgrastim biosimilars, for example, the EMA allowed for extrapolation from the indication neutropenia to the indication of stem cell mobilization in healthy donors. The concerns of clinicians could be disproved by post-marketing studies, which confirmed the biosimilars' safety and efficacy in the latter indication. In the case of epoetin biosimilars, it was questioned whether confirmatory clinical studies in renal anaemia were sensitive enough to justify an extrapolation to chemotherapy-induced anaemia in cancer patients. Again, post-marketing studies could clearly answer this question in favour of EMA's extrapolation decision. And with regard to the ongoing debate on the extrapolation of infliximab biosimilars from rheumatoid arthritis (RA) to inflammatory bowel disease (IBD), EMA regulators do not deny that there is indeed a 20% difference in antibody-dependent cellular cytotoxicity activity between originator and biosimilar in the most sensitive in vitro assay. Yet they emphasize that this difference has not been observed in more physiologically relevant assays. [Weise 2014 and 2016]

In addition to this biosimilar related experience, regulators clearly point out that – in a strict sense – they have granted kind of extrapolation of indications many times already to the originator biologicals themselves. They underline that every change in the manufacturing process of a biological results in a structurally slightly different version of the original. They stress that therefore in relation to manufacturing changes every biological product and hence the originator biologicals, too, has to undergo the same comparability exercise, which is required for establishing biosimiliarity to demonstrate that their same safety and efficacy is not altered by the change. And this applies practically to all indications they are approved for. In a way, each biological thus frequently becomes a biosimilar to itself (the only difference to "real" biosimilars remains the manufacturer's profound knowledge of his proprietary manufacturing process). All in all, 404 such manufacturing changes for 29 registered original mAbs have occurred to date,

according to the publicly available EPAR reports. The manufacturing process for the originator infliximab alone as of 2013 had already changed 50 times since its approval; of them 3 of were categorized as "high risk" manufacturing changes, 13 as "moderate risk", and 34 as "low risk" changes according to the information provided with the EPAR. [Vezer 2016]

Due to its pioneering role in the approval of biosimilars, the EMA has gathered more experience with the extrapolation of indications than others. As described earlier in this thesis, many regulatory authorities around the world built on EMA's experience and expertise in this respect and share its positive attitude towards extrapolation of indications. Health Canada, on the other hand, in the case of infliximab biosimilars did not follow EMA's example. The Canadian agency certainly attempted to be very cautious because it had actually no experience with biosimilars before: Its approvals of two infliximab biosimilars in January 2014 were its first biosimilar approvals at all after it had issued its "Guidance for sponsors: Information and submission requirements for subsequent entry biologics" in March 2010. It had approved, however, one somatropin biosimilar prior to the publication of this guideline in April 2009.

Nevertheless, according to one of its representatives, the Canadian authority was uncertain how to best deal with the extrapolation of indications due to the fact that "scientific and regulatory knowledge and experience are limited in dealing with these types of issues" and that – with regard to the extrapolation from RA to IBD – the „pre-submission package was not sufficiently informative in terms of the issue of concern" [Wang, quoted by GaBI 2015]. Referring to the insufficient information, one can indeed speculate that Health Canada based its decision on a different and less informative package than the EMA. According to the Summary Basis of Decision of the Canadian EPAR [HC-SBD 2014], the Canadian data package for the regulatory review of Inflectra contained Celltrion's responses to EMA's "Day 120 and Day 180 List of Questions as an added reference, particularly for assessing immunogenicity as more information was provided by the sponsor to address CHMP questions" [HC-SBD 2014]. According to EMA's documentation of the steps taken for the assessment of Inflectra, however, there was at least one list of outstanding issues, which had been addressed by the EMA and answered by Celltrion after the reception of the responses to the Day 180 List of Questions [EMA EPAR 2015]. It remains to be seen, of course, if Health Canada perhaps will revise its decision should post-marketing studies confirm the safe and effective applicability of Infliximab biosimilars in IBD. The disagreement between Health Canada and most other regulatory agencies with regard to the application of infliximab biosimilars in the treatment of IBD considerably contributes to the concerns of clinicians and even reinforces them.

Independent from this, however, it is important to ask why clinicians and their learned societies have such a different viewpoint than regulators when it comes to judging the entitlement for an extrapolation of indications for biosimilars. Clinicians are certainly right when they worry about safety because of different immunogenic profiles and about efficacy because of different post-

glycosylation patterns between originator and biosimilar. Yet regulators worry about these issues, too. They only judge them from a more holistic perspective. While clinicians tend to focus on the clinical part of the evaluation of a biosimilar only, regulators refer to the "totality of evidence" when deciding on the approval of a biosimilar. They see the analytical and non-clinical tests and the clinical trials as one package. Clinicians tend to underestimate the scope, precision and validity of the comparative head-to-head analytical tests, which a biosimilar has to pass before it is approved and before the regulatory authorities deem extrapolation of indications appropriate. Clinicians of course know that for the approval of an originator product mode of action, pharmacology and toxicology have to be investigated in detail – and somewhat intuitively demand this from a biosimilar, too. For a biosimilar, however, these things are already known. A biosimilar is not, as many clinicians think, a new drug. It rather contains a new version of the active substance of the originator product.

Clinicians gain their confidence in a new drug primarily from the results of clinical trials. They are sceptic about preclinical comparability exercises. Yet regulators rightly emphasize the crucial importance of those PK/PD studies for the successful development of a biosimilar. They urge the biosimilar sponsor not to enter a clinical trial before comparability has not been demonstrated. They demand that such a trial is conducted in an indication that is representative for other indications and sensitive for showing differences. To them, trials in all therapeutic indications appear neither to be necessary nor feasible.

Under regulatory perspective, the clinical trial of a biosimilar has no other purpose but to complement and confirm the previously demonstrated comparability. In other words: The trial has to proof nothing else but comparability or non-inferiority. Accordingly, the clinical endpoints of the biosimilar trial mostly differ from those for the pivotal approval trials of the originator. They need to be more sensitive. In a clinical study with an originator product in an oncological indication, for example, primary endpoints would generally be overall survival rate and time to progression. To determine these endpoints takes a rather long time. To evaluate the comparability of a biosimilar, therefore a more reasonable endpoint is advisable, such as overall response rate.

Under these circumstances, it is particularly for clinicians specialized in one therapeutic area (such as the members of learned societies) difficult to accept that studies performed in one disease can be applied to another disease with different pathogenic features. For regulators, however, this is not an unusual approach. They are not so much focused on pathogenesis but rather rely on receptor binding and functional tests of the biosimilar, i.e. the mode of action of the active substance [Kurki 2016].

Despite the different viewpoints of clinicians and regulators, the acceptance of biosimilars among physicians obviously is slowly but steadily increasing. While infliximab biosimilars between January and September 2015 represented only 8% of the total German infliximab

market, the much earlier launched filgrastim biosimilars during the same period represented already 64% of the total German filgrastim market. All approved biosimilars took a share of 19% of the German market for biologicals that had already lost their patent protection at this time. [Daubenfeld 2016] Nevertheless, physicians still are not sufficiently informed about biosimilars, and remain reluctant to prescribe them. At a recent roundtable discussion involving European regulators and clinicians, however, clinicians pointed out that some of their concerns about extrapolation of indications had already been relieved by results from open label studies, which biosimilar sponsors had conducted voluntarily, and that they hoped to see more of such studies in the future. Regulators, on the other hand, tried to convince clinicians of another advantage of extrapolation. Because a limited set of therapeutic indications may lead to off-label use, they argued, it would be desirable from the pharmacovigilance point of view, if all biosimilars in the EU were approved in the same therapeutic indication as their originator product [Giezen 2016].

6. Conclusion

No other feature of biosimilars is nearly as attractive as the possibility to extrapolate from one indication of the originator to all others. It is the single greatest benefit of biosimilar development, both for pharmaceutical companies and for health care providers. For the former it saves development resources and lowers market entry barriers to the lucrative market of biologicals, for the latter it substantially decreases its expenditure and thus increases affordability.

At the same time, extrapolation of indications is the most controversial issue in biosimilar development. Of course this has to do with factual challenges, such as naturally occurring structural differences between an originator biological and its biosimilar, which might affect safety and efficacy. More so, however, it has to do both with a considerable knowledge gap and a different paradigm in judging drugs between regulators and clinicians. As this thesis has shown, regulatory authorities, especially the EMA, have been at the cutting edge of implementing guidelines for the extrapolation of indications for biosimilars for long. They have gained enough experience to see the issues at stake relatively relaxed, trusting in the scientific soundness of their principles and the thoroughness of their assessments. Clinicians and their learned societies, respectively, initially did not show much interest in biosimilars and their extrapolation. Their interest became only more intense when the first monoclonal antibody biosimilar was approved. This class of biologicals is more complex than any other, so clinical concerns are certainly justified. Yet it is also more lucrative than any other, so sometimes it is difficult to tell whether clinicians are subject to conflicts of interest, be it on the side of the originator or the biosimilar manufacturer. Regulators in this respect can be regarded as more objective. It belongs to their responsibility to help educate clinicians, physicians and patients about biosimilars and their appropriate use.

The current discussion resembles the one, which took place about 30 years ago, when regulators paved the way for the introduction of chemically-synthesized generics. The interests of original and generic manufacturers collided, clinicians, partly objective, partly not, raised their concerns, prescribers were reluctant and patients puzzled. It took some time to overcome this situation and to close the knowledge gap between regulators and all other stakeholders of the health care system. Today, generics are an indispensable part of all health care systems. Even if they are much more complex, biosimilars can be expected to take the same development, including their extrapolated indications.

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Annex 1 Extrapolation in EMA biosimilar guidance

EMA – Overarching biosimilar guidelines

- Similar biological products (2005) - rev.1 (2014)
- … non-clinical and clinical issues (2006) – rev.1 (2015)

EMA - Product-specific biosimilar guidelines

- recomb. Follicle-stimulating hormone (r-hESH) (Feb.2013)
- Interferon-beta (Feb 2013)
- mAbs (May 2012)
- recomb. Erythropoietins (Apr 2010)
- LMWH (Apr 2009) – rev. draft for comments 2013

EMA – Overarching biosimilar guidelines

437/04 **Similar biological medicinal products** (2005)	NO	***2005***
437/04 rev.1 **Similar biological medicinal products** (Okt.2014)	**3. General principles** **3.1. Application of the biosimilar approach** If biosimilarity has been demonstrated in one indication, **extrapolation to other indications** of the reference product could be acceptable with appropriate scientific justification … **3.3 Principles of establishing biosimilarity** … In specific circumstances, a confirmatory clinical trial may not be necessary. This requires that similar efficacy and safety can clearly be deducted from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and the reference product. In addition, it requires that the impurity profile and the nature of excipients of the biosimilar itself do not give rise to concern. It is recommended to discuss such simplified approaches with Regulatory Authorities.	***2014***

Overarching Biosimilar Guideline		
42832/2005 S b m p containing biotechnology-derived proteins as active substance: **non-clinical and clinical issues** (2005)	**1. Introduction** … in case the originally authorized medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be **justified or**, if necessary, **demonstrated separately for each of the claimed indications.** In **certain cases it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product**. Justification will depend on e.g. clinical experience, available literature data, whether or not the same mechanisms of action or the same receptor(s) are involved in all indications. Possible safety issues in different subpopulations should also be addressed. In any case, the company should justify the approach taken during the development of the product and might want to contact the EMEA before starting the development for scientific and regulatory advise.	***2005***
42832 rev.1 S b m p containing biotechnology-derived proteins as active substance: **non-clinical and clinica**l issues (Dec.2014)	**Extensive summary** The current revision covers the following topics: a stepwise approach for the design of non-clinical studies; the use of PD markers; study design, choice of appropriate patient population and choice of surrogate and clinical endpoints in efficacy trials; clinical safety (including design of immunogenicity studies), risk management plan, and pharmacovigilance, and **extrapolation of safety and efficacy**. The guideline recommends a stepwise conduct of non-clinical and clinical studies **6. Extrapolation of efficacy and safety from one therapeutic indication to another** The reference medicinal product may have more than one therapeutic indication. When biosimilar comparability has been demonstrated in one indication, **extrapolation** of clinical data to other indication of the rp could be acceptable but needs to be scientifically justified. In case it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication, additional data will be required. **Extrapolation should be considered in the light of the totality of data,** i.e. quality, non-clinical and clinical data. It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by thorough physico-chemical and structural analyses as well as by in vitro functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication. Additional data are required in certain situations, such as 1. the active substance of the r p interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indication 2. the active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications 3. the studied therapeutic indication is not relevant for the others in terms of efficacy or safety, i.e. is not sensitive for differences in all relevant aspects of efficacy and safety. Immunogenicity is related to multiple factors including the route of administration, dosing regimen, patient-related factors and disease-related factors (e.g. co-medication, type of disease, immune status. Thus, immunogenicity could differ among indications. **Extrapolation of immunogenicity** from the studied indication/route of administration to other uses of the reference product should be justified.	***2014***

EMA - Product-specific biosimilar guidelines

Extrapolation in EMA Biosimilar guidelines		
671292/2010 Sbmp containing recombinant follicle-stimulating hormone (**r-hFSH**) (Feb.2013)	**1. Executive summary** … Criteria for extrapolation of clinical data to other indications approved for the reference medicinal product are discussed. **6. PV** … The RMP of the biosimilar should take into account identified and potential risks associated with the use of the reference product and, if applicable, safety in indications licensed for the reference product that are claimed based on extrapolation. In addition, it should be discussed in detail how these safety concerns will be addressed in post-marketing follow-up. **7. Extrapolation of indication** Demonstration of similar efficacy and safety of the test compared to the reference product for stimulation of multifollicular development in patients undergoing superovulation for ART will allow extrapolation to other therapeutic indications approved for the reference product.	***2013***
652000/2010 … **interferon-beta** (Feb.2013)	**4.2 Clinical Studies – Clinical Efficacy** … The equivalence margin for the primary MRI endpoint should be pre-specified and adequately justified based on MRI data for the reference medicinal product relative to placebo, or if not available, extrapolation from other IFN-β relevant da **4.4. Extrapolation of indication** Extrapolation of clinical efficacy and safety in confirmed RRMS to the other indications of the reference medicinal product in MS is possible on the basis of the totality of the evidence provided from the comparability exercise…	***2013***
301636/2008 Corr.*, 2010 …. Non-clinical and clinical development … **recombinant erythropoietins** (Apr 2010)	**Executive summary** Criteria for extrapolation of clinical data to other indications approved for the reference medicinal product are discussed. **4.5 Extension of Indications** (4. Main Guideline text) Since the mechanism of action of epoetin is the same for all currently approved indications and there is only one known epoetin receptor, demonstration of **efficacy and safety in renal anaemia will allow extrapolation to other indications** of the reference medicinal product with the same route of administration.	***2010***
945626/2005..Annex to …guidance on sbmp containing recombinant *erythropoietins* (March 2006)	*The electronic version of this document is currently unavailable*	***2006***
403543/2010 …	**1. Executive summary** During the clinical development programme, patients are usually enrolled commensurate with the level of evidence obtained from	***2012***

Extrapolation in EMA Biosimilar guidelines		
monoclonal antibodies (**mABs**): non-clinical and clinical issues (May 2012)	preceding steps which support comparability. A comparative pharmacokinetic study in a sufficiently sensitive and homogeneous study population (healthy volunteers or patients) normally forms an initial step of biosimilar mAb development. PK data can be helpful to **extrapolate data on efficacy and safety between different clinical indications** of the reference mAB. It may, on a case-by-case basis, be necessary to undertake multidose PK studies in patients, or even to perform PK assessment as part clinical study designed to establish similar efficacy and safety. … **Extrapolation of clinical efficacy and safety data to other indications** of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, is **possible based on the results of the overall evidence provided from the comparability** exercise and with adequate justification. As regards post-authorisation follow-up, the concept to be proposed by applicants may have to exceed routine pharmacovigilance, and may have to involve post-authorisation safety studies (PASS). … **6. Extrapolation of indications** Extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, is possible **based on the overall evidence of comparability provided from the comparability exercise and with adequate justification**. If pivotal evidence for comparability is based on PD and for the claimed indications **different mechanisms of action are relevant (or uncertainty exists**), then applicants should **provide relevant data to support extrapolation** to all claimed clinical indications. Applicants should support such extrapolations with a **comprehensive discussion of available literature including the involved antigen receptor(s) and mechanism(s) of action.** For example, if a reference mAb is licensed **both as an immunomodulator and as an anticancer antibody**, the scientific justification as regards extrapolation between the two (or more) indications **is more challenging**. The basis for such extrapolation forms an extensive quality and non-clinical database, including potency assay(s) and in vitro assays that cover the functionality of the molecule, supplemented by relevant clinical data as described further in this document. The **possibility of extrapolating safety including immunogenicity** data also requires careful consideration, and may have to involve more specific studies (see Sections 5 ClinSt and 7 PV). For the mechanism of action, e.g. the depletion of immune cells, **several mechanisms may play a role in the various clinical conditions.** For example, ADCC appears to be more important in some indications than in others. To provide further evidence about the mechanism of action, it may also be helpful to perform a literature search to identify what is known, e.g. about potential signalling inhibition by the reference mAb that would not be covered by ADCC/CDC tests, in particular direct induction of apoptosis. This could provide more knowledge on potential read-outs that could be used to support comparability on a molecular level. **7. PV**	

Extrapolation in EMA Biosimilar guidelines		
	…Further to safety considerations as discussed above, applicants should provide at the time of MAA a comprehensive concept how to further study safety in a post-authorisation setting including also the following aspects: • **Safety in indications licensed** for the reference mAb that are claimed **based on extrapolation of efficacy and safety data**, including long term safety data unless otherwise justified.	
118264/2007 …sbmp containing low molecular weight heparins **(LMWH)** (Apr 2009)	**6. EXTRAPOLATION OF INDICATION** Demonstration of comparable efficacy and safety **in surgical patients at high risk for VTE** as recommended **may allow extrapolation** to other indications of the reference medicinal product if appropriately justified by the applicant.	***2009***
118264/2007 rev.1 Non-clinical and clinical dev. of sbmp containing **LMWHs** draft guideline comments deadline 31 Jul 2013	6. Pharmacogivilance … The RMP of the biosimilar should take into account identified and potential risks associated with the use of the reference product and, if applicable, safety in indications authorised for the reference product that are **claimed based on extrapolation** … **7. Extrapolation of indication** Demonstration of comparable efficacy and safety **in surgical patients at high risk for VTE** as recommended or **by other means as described above may allow extrapolation to other indications** of the reference medicinal product if appropriately justified by the applicant. From the recommendations of the preceding Concept paper EMA/CHMP/BMWP/522386/2011: "As part of this revision, the Working Party recommends a discussion about including the possibility of a modification in clinical data requirements, providing similarity of physicochemical characteristics of the biosimilar and the reference LMWH has been convincingly shown and similar efficacy and safety can be ensured by other means. At the same time there should be a discussion if for the non-clinical part a risk-based approach should be introduced as currently discussed for other biosimilar product"	***2013***
94528/2005 Annex …-recomb. **Insulin** Insulin analogues (Feb 2006)	*NO*	***2006***
32775/2005 rev.1 …non-clin/clin dev sbmp cont recomb. **Insulin and Insulin analogues**	**7. Extrapolation of indication** Demonstration of biosimilarity based on the physicochemical and functional characterisation, the pharmacokinetic and, where needed, **pharmacodynamic** profiles and **absence of safety issues with subcutaneous** use will allow extrapolation to **intravenous** use, if applicable, and to **other indications and patient populations** licensed for the reference product	***2015***

Extrapolation in EMA Biosimilar guidelines		
(March 2015)		
102046/2006 Reflection paper /Adopt. GL: Non-clin/clin dev of sbmp containing recomb **interferon alpha** (Jun 2009)	6. EXTRAPOLATION OF EVIDENCE In principle extrapolation from one therapeutic indication to another is appropriate where the mechanism of action and/or the receptor are known to be the same as the condition(s) for which similarity in efficacy has been established. If indication(s) are sought, where the mechanism of action is not known to be the same, such extrapolation should be adequately justified.	***2009***
/693108/2015 … Concept paper on the revision of the reflection paper…Dez 2015 … **interferon alpha or pegylated** interferon alpha comments deadline March 2016	… Reflection paper (*to be revised)* was published in April 2009. Since then, no products containing biosimilar interferon alpha have been licensed in the EU *NO hint to extrapolation of indications, but proposal to skip confirmatory clinical trial. Thus, the biosimilar might gain all indications of the reference product without any clinical pivotal trial …* 3. Discussion on the problem statement 1… 2. The focus of the non-clinical comparability exercise is on in vitro studies, which are usually more specific and sensitive to detect differences between the biosimilar and the reference product than in vivo studies. For this reason and to avoid unnecessary animal studies, a **risk-based approach is now generally accepted**. It is suggested to adapt the reflection paper on biosimilar interferon alpha containing products along these lines of thinking 3. The revised "overarching" Guideline … (CHMP/437/04 Rev.1) states prerequisites for **waiving clinical trials**. These conditions may be accomplishable for biosimilar interferon alpha since structure, physicochemical characteristics and biological activity of interferon alpha are well characterisable by state of-the art methods and PD parameters of clinical relevance are available. Regulatory expectations to support a biosimilar recombinant interferon alpha development without a confirmatory clinical trial will need to be further discussed and included in the guideline	***2016***
94528/2005 Annex …-**somatropin (**Feb 2006)	4.5 EXTENSION OF INDICATION Demonstration of efficacy and safety in GH-deficient children may allow extrapolation to other indications of the reference medicinal product if appropriately justified by the applicant.	***2006***
/945626/2005 Annex … **recomb**	**Clinical efficacy studies**	***2006***

Extrapolation in EMA Biosimilar guidelines		
granulocyte-colony stimulat. factor (rhG-CSF) (Feb 2006)	Demonstration of the clinical comparability in the **chemotherapy-induced neutropenia model** will allow the extrapolation of the results to other indications of the reference medicinal product, if the mechanism of action is the same	
214262/2015 Concept paper released for consultation non-clin/clin dev. sbmp containing **rhG-CSF** (Jul 2015) comments deadline Oct 2015	guideline *(to be revised)* was one of the first product-class specific biosimilarity guidelines and came into effect in February 2006. Since then, several biosimilar filgrastims have been licensed in the EU. … *NO hint to extrapolation of indications, but proposal to skip confirmatory clinical trial. Thus, the biosimilar might gain all indications of the reference product without any clinical pivotal trial …* 3. Discussion on the problem statement 1… 2. The focus of the non-clinical comparability exercise is on in vitro studies, which are usually more specific and sensitive to detect differences between the biosimilar and the reference product than in vivo studies. For this reason and to avoid unnecessary animal studies, a risk-based approach is now generally accepted. . It is suggested to adapt the guideline on biosimilar rhG-CSF containing products along these lines of thinking 3. The revised "overarching" Guideline … (CHMP/437/04 Rev.1) states prerequisites for waiving clinical trials. These conditions may be accomplishable for biosimilar rhG-CSG since structure, physicochemical characteristics and biological activity of rhG-CSG are well characterisable by state of-the art methods and PD parameters of clinical relevance are available. Regulatory expectations to support a biosimilar rhG-CSG development without a confirmatory clinical trial will need to be further discussed and included in the guideline	***2016***

Annex 2

Annex 2: Guideline excerpts regarding „Extrapolation of indications for biosimilars”

Overview:

Region:	**Europe (1)**
Title:	**Similar biological medicinal products** (CHMP/437/04, rev.1) of October 2014, effective 30 April 2015
Access:	
Date:	**2014**
Text:	3. General principles – 3.1. Application of the biosimilar approach … In principle, the concept of biosimilarity is applicable to any biological medicinal product. However, in practice, the success of developing a biosimilar will depend on the ability to produce a medicinal product which is similar to the reference medicinal product, and to convincingly demonstrate the similar nature of the concerned products. This includes comprehensive physicochemical and biological characterisation and comparison and requires knowledge on how to interpret any differences between a biosimilar and its reference medicinal product. Therefore: … • If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification.

Region:	**Europe (2)**
Title:	**Similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues** (EMEA/CHMP/BMWP/42832/2005, rev.1) 18 Dec 2014
Access:	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf
Date:	**2014**
Text:	**Extensive summary** The current revision covers the following topics: a stepwise approach for the design of non-clinical studies; the use of pharmacodynamic markers; study design, choice of appropriate patient population and choice of surrogate and clinical endpoints in efficacy trials; clinical safety (including design of immunogenicity studies), risk management plan, and pharmacovigilance, and **extrapolation of safety and efficacy**. The guideline recommends a stepwise conduct of non-clinical and clinical studies **6. Extrapolation of efficacy and safety from one therapeutic indication to another** The reference medicinal product may have more than one therapeutic indication. When biosimilar comparability has been demonstrated in one indication, **extrapolation** of clinical data to other indication of the rp could be acceptable but needs to be scientifically justified. In case it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication, additional data data will be required. **Extrapolation** should be considered in the light of the totality of data, i.e. quality, non-clinical and clinical data. It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by thorough physico-chemical and structural analyses as well as by in vitro functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication. Additional data are required in certain situations, such as 4. the active substance of the r p interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indication 5. the active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications 6. the studied therapeutic indication is not relevant for the others in terms of efficacy or safety, i.e. is not sensitive for differences in all relevant aspects of efficacy and safety. Immunogenicity is related to multiple factors including the route of administration, dosing regimen, patient-related factors and disease-related factors (e.g. co-medication, type of disease, immune status. Thus, immunogenicity could differ among indications. **Extrapolation of immunogenicity** from the studied indication/route of administration to other uses of the reference product should be justified.

Region:	**WHO**
Title:	**Guidelines On Evaluation Of Similar Biotherapeutic Products (SBPS)** Geneva, 19 to 23 October 2009
Access:	http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf
Date:	**2009**
Text:	**5 Scientific considerations and concept for licensing SBPs** (page 8) …If similarity between the SBP and the RBP has been convincingly demonstrated, the SBP may be approved for use in other clinical indications of the RBP that have not directly been tested in clinical trials if appropriate scientific justification for such extrapolation is provided by the manufacturer (see section 10.7) **10. Clinical evaluation ….** (page 23) …An additional advantage of demonstration of equivalent efficacy (rather than non-inferior efficacy) is that this would provide a stronger rationale for the possibility of extrapolation of efficacy data to other indications of the RBP, particularly if these include different dosages than the one(s) tested in the clinical trial (see section 10.7). **10.7 Extrapolation of efficacy and safety data to other clinical indications** If similar efficacy and safety of the SBP and RBP have been demonstrated for a particular clinical indication, extrapolation of these data to other indications of the RBP (not studied in independent clinical studies with the SBP) may be possible if all of the following conditions are fulfilled: • A sensitive clinical test model has been used that is able to detect potential differences between the SBP and the RBP; • The clinically relevant mechanism of action and/or involved receptor(s) are the same; e.g. GH action in different conditions of short stature in children; erythropoiesis-stimulating action of epoetins in different conditions associated with anaemia or for the purpose of autologous blood donation. If the mechanism of action is different or not known a strong scientific rationale and additional data (e.g. "PD fingerprint", additional clinical data) will be needed; • Safety and immunogenicity of the SBP have been sufficiently characterized and there are no unique/additional safety issues expected for the extrapolated indication(s), for which clinical data on the SBP are not being provided; e.g. immunogenicity data in immunosuppressed patients would not allow extrapolation to an indication in healthy subjects or patients with autoimmune diseases while the reverse would be valid; • • If the efficacy trial used a non-inferiority study design and demonstrated acceptable safety and efficacy of the SBP compared to the RBP, the applicant should provide convincing arguments that this finding can be applied to the extrapolated indications; e.g. results from a non-inferiority trial in an indication where a low dose is used may be difficult to extrapolate to an indication where a higher dose is used, from both efficacy and safety point of view. If these prerequisites for extrapolation of efficacy and safety data of the SBP to other indication(s) of the RBP are not fulfilled, the manufacturer will need to submit own clinical data to support the desired indication(s). If extrapolation of results from clinical studies for one indication to one or more different indications is intended, a detailed scientific discussion on the benefit/ risk of such a proposal should be provided based on the above criteria.
Label:	**12 Prescribing information and label** The SBP should be clearly identifiable by a unique brand name. Where an INN is defined,

Region:	WHO
	this should also be stated. WHO policy on INNs should be followed (http://www.who.int/medicines/services/inn/innquidance/en/index.html). Provision of the lot number is essential as this is an important part of production information and is critical for traceability in cases where problems with a product are encountered. The prescribing information for the SBP should be as similar as possible to that of the RBP except for product-specific aspects, such as different excipient(s). This is particularly important for posology and safety-related information, including contraindications, warnings and adverse events. However, if the SBP has fewer indications than the RBP, the related text in various sections may be omitted unless it is considered important to inform doctors and patients about certain risks; e.g. because of potential off-label use. In such cases it should be clearly stated in the prescribing information that the SBP is not indicated for use in the specific indication(s) and the reasons why. The NRA may choose to mention the SBP nature of the product and the studies that have been performed with the SBP including the specific RBP in the product information and/or to include instructions for the prescribing physician on how to use SBP products.

Region:	**Canada**
Title:	**Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEB) -** Draft Date 2010/03/05 Draft - **Revised Guidance Document –** Draft Date: 2015-08-13, Release for Consultation: 2015-12-07
Access:	http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/seb-pbu/seb-pbu_2010-eng.php Draft for consultation: http://www.hc-sc.gc.ca/dhp-mps/consultation/biolog/submission-seb-exigences-pbu-eng.php
Date:	**2010** **Rev. 2015** (Draft, end-of-consultation 15-Feb-2016)
Comment:	New draft contains a **definition of extrapolation**, which was not in the previous guidance Section 2.3.3, *Non-Clinical and Clinical Information*: Additional detail is provided with respect to considerations when performing non-clinical and clinical studies for SEBs, including discussion with respect to immunogenicity, the use of the most sensitive population in clinical trial design and a new section on extrapolation
Text:	Revision in texts highlighted: current / ~~deleted in revision~~ / new in revision **2.3.2 Non-clinical and Clinical Information** **2.3.2.1 General**…An SEB product sponsor is eligible to apply for one or more clinical indications granted to the reference biologic drug in Canada. Any claims made by the SEB sponsor should be supported by suitable scientific data, which should typically include safety and efficacy data generated with the SEB. ~~However~~, in some situations, proposals for additional indications held by the reference biologic drug via extrapolation, as outlined in section 2.3.3.4 may be considered ~~granted to~~ for the SEB in the absence of such clinical data. In other situations, ~~some cases~~, comparative pharmacokinetic/pharmacodynamic (PK/PD) data to bridge two or more indications may be sufficient. ~~It may also be possible to extrapolate clinical data to other indications where rationales are sufficiently persuasive. The extrapolation should be justified based on: mechanism(s) of action; pathophysiological mechanism(s) of the disease(s) or conditions involved; safety profile in the respective conditions and/or populations; and clinical experience with the reference biologic drug. A detailed scientific rationale that addresses appropriately the benefits and risks of such a proposal should be provided to adequately support the data extrapolation.~~ Where a clinical indication being sought is not held by the reference biological drug, full clinical trial data should be provided in support of that indication in order to meet the requirements outlined in Part C. Division 8 of the *Food and Drug Regulations*. … The design of comparative pharmacokinetic studies (e.g. cross-over study versus parallel study) should take the following factors into considerations: • half-life of the biologics; • linearity of PK parameters; • where applicable, the endogenous levels and diurnal variations of the protein under study; • conditions and diseases to be treated; • route(s) of administration; and • indications for which the SEB sponsor is applying. Results from healthy subjects may not adequately reflect the PK parameters in the patient population where the product is indicated. Therefore, it is best to conduct the studies in the relevant patient population. However, where it is justifiable and where there is no undue risk, PK studies may be conducted in healthy subjects. Dose(s) used in the PK studies should be within the therapeutic dosing range specified in the Product Monograph (PM) of the reference biologic drug. ….

Region:	Canada
	Demonstration of non-inferiority of an SEB to the reference biologic drug might not provide strong support for the extrapolation to other indications, particularly if the other indications include different dosages than those tested in the clinical trial **2.3.3.4. Extrapolation** Once similarity has been established, based on the physicochemical structure, biological activity, PK/PD and clinical studies, it may be possible to extrapolate clinical data from one indication to other indications where rationales are provided. Extrapolation should be justified based on: mechanism(s) of action; pathophysiological mechanism(s) of the disease(s) or conditions involved; safety profile in the respective conditions and/or populations; and, clinical experience with the reference biologic drug. A detailed scientific rationale that appropriately addresses the benefits and risks of such a proposal should be provided to adequately support the data extrapolation. Health Canada also recommends that SEB sponsors consider how the following aspects of their comparative clinical program relate to the indications for which authorization would require extrapolation (i.e. when there is an intention to request the authorization of additional indications without indication specific data): • The characteristics of the studied population(s); • The characteristics of the clinical trials, such as study duration, route of administration, and dosage regimen; • The risk and impact of immunogenicity; and • The impact of concomitant therapies on the relevance of the data to indications and clinical uses requested via extrapolation (i.e. monotherapy vs. combination therapy). As the above mentioned considerations may not take into account other elements including some of the factors on comparability and mechanism of action for some of the indications and clinical uses, some case by case considerations may apply. Sponsors are encouraged to contact BGTD when considering the extrapolation of clinical data to other indications.
Label:	**2.5 Labelling requirements (Product Monograph)** Unlike generic pharmaceutical drugs, the sponsor of an SEB will not be able to utilize the PM of the reference biologic drug in its entirety as that of its own product. The PM for an SEB should be developed in a manner consistent with the principles, practices, and processes outlined in the "Guidance for Industry: Product Monograph(2004)". The contents of the PM for SEBs will include following information: • A statement indicating that the product is an SEB[2] • Key data on which the decision for market authorization was made • Tables showing the results of the comparisons between the SEB and reference biologic drug • Information on the indications approved for use • There should be no claims for bioequivalence between the SEB and reference biologic drug • There should be no claims for clinical equivalence between the SEB and the reference biological drug

Region:	**Japan**
Title:	**Guideline for the Quality, Safety, and Efficacy Assurance of Follow -on Biologics** PFSB/ELD Notification No. 0304007 March 4, 2009 (provisional tranlastion as of April 19, 2013)
Access:	Transl:http://www.pmda.go.jp/files/000153851.pdf
Date:	**2009**
Other text:	**2. Scope** This guideline covers recombinant proteins and polypeptide products (including simple protein and glycoprotein products), their derivatives, and products of which they are components, e.g., conjugates. Such proteins and polypeptides are produced from recombinant expression systems using microorganisms or cultured cells and can be highly purified and well-characterized using an appropriate set of analytical procedures ... This guideline is not applicable to antibiotics, synthetic peptides/polypeptides, polysaccharides, vitamins, metabolic products of cells, nucleic acid products, allergen extracts, conventional vaccines based on antigens such as attenuated or inactivated pathogenic microorganisms and extracts, cells or whole blood/cellular blood components (blood cell components).
Text:	**8. 2 Comparison of clinical efficacy** Even though high similarity in quality has been demonstrated through comparability studies on the quality attributes, an analysis of all data from the PK, PD or PK/PD studies might not demonstrate the comparability of clinical efficacy. In this case, it is necessary to conduct clinical studies to verify that the efficacy of the follow-on and originator biologics in respect of the indications of the product for which approval is sought are comparable. In the case of an original biologic with more than one indication, if the efficacy and pharmacological effects of the follow-on biologic have been demonstrated to be comparable to one of the indications of the original biologic and comparability of pharmacological effects on the Other indications can be expected , then in certain case , it may be possible to extrapolate from one approved indication to the other approved indications of the original biologic used as the reference product. The extrapolation of indications is limited to the indications of the reference original biologic and does not include the indications of other approved recombinant protein products with similar indications. However, where each relevant indication have a different mechanism of action or the mechanism of each indication remains unclear, the comparability of efficacy with the original biologic should be demonstrated for each indication, without extrapolation.
Japan	Not evaluated

Region:	**Korea**
Title:	Secondary source: Joung, Jeewon: **Korean regulations for biosimilars** Generics and Biosimilars Initiative Journal (GaBI Journal) 4(2015)2, 93-94
Access:	http://gabi-journal.net/korean-regulations-for-biosimilars.html
Date:	**2014**
Other	**Interchangeability** Unlike small-molecule chemical generics, automatic substitution of biosimilars at the pharmacy level is not allowed in South Korea
Text:	**Extrapolation of indications** In South Korea, if similar efficacy and safety of the biosimilar and the reference product have been demonstrated for a particular clinical indication, then the biosimilar product may receive authorization for other indications of the reference product. The extrapolation of clinical indications of a biosimilar product is allowed for indications where the post-marketing surveillance period of the reference product has expired and if all of the following conditions are fulfilled: • A sensitive clinical test model to detect potential differences (between the biosimilar and the reference product) is used • The clinically relevant mechanisms of action and the involved receptors are the same for the different indications • The safety and immunogenicity have been sufficiently characterized

Region:	**Israel**
Title:	Work procedure No. 127 of 1 April 2014 **"Policy regarding Registration and Use Conditions of Bio-Similar Pharmaceuticals"** Secondary source: Newsletter provided by Reinhold Cohn Group.
Access:	http://www.rcip.co.il/en/article/a-new-policy-regarding-the-registration-and-use-of-bio-similar-pharmaceuticals-in-israel/
Date:	**2014**
Comment:	Up until the issuance of Work Procedure 127, the MoH (Ministry of Health) operated through an internal guideline[3], according to which bio-similar pharmaceuticals could be registered with the MoH if they had been previously registered with the European Medicines Agency (EMA) via the "Bio-Similar" route, or with the US Federal Drug Administration (FDA) via the "Follow on Protein Products" route[4]. Each application was to be considered on a case-by-case basis. … In general, according to the Work Procedure, the MoH adopts EMA policies in the relevant issues at hand, relating to Bio-Similar Pharmaceuticals, customized to the need of the State of Israel. [3] *The internal guideline was published in the form of a letter to the pharmacists-in-charge of registration owners, dated March 31st, 2009.* [4] *Under certain conditions as follows: (1) all data filed with the EMA or FDA should be filed together with the registration application; (2) the original pharmaceutical is registered in the Israeli Registry of Pharmaceuticals, and contains the identical active substance of the pharmaceutical applied for registration*
Text:	**Indications for Bio-Similar Pharmaceuticals** Specific provisions of the Work Procedure also refer to the approval of indications for a Bio-Similar Pharmaceutical. Indications of a Bio-Similar Pharmaceutical will be approved only if: **(i)** They are approved also for the Reference Medicinal Product; **(ii)** They were tested in clinical trials of the Bio-Similar Pharmaceutical; **(iii)** They were approved (for the Bio-Similar Pharmaceutical) by the EMA and/or FDA. Extrapolations from indications for a Reference Medicinal Product, being an exception to the foregoing general rule, will be allowed only if the biological mechanism of action of the Bio-Similar Pharmaceuticals and of the Reference Medicinal Product are identical.
Label	**Labeling of a Bio-Similar Pharmaceutical** The issue of labeling a Bio-Similar Pharmaceutical is also addressed in the Work Procedure, according to which a Bio-Similar Pharmaceutical must be labeled in a clearly identifying manner, so as to distinguish it from other biological pharmaceuticals . In addition, the commercial name followed by the active ingredient name in parenthesis should be indicated on the label, on the leaflet, in the drug registry, and in the drug information databases.

Region:	**India**
Title:	**Guideline on "Similar Biologics: Regulatory requirements for Market Authorization in India" (**implemented 15th Sept, 2012, 52 pages) **Guidelines on Similar Biologic: Regulatory Requirements for Marketing Authorization in India** (proposed March 2016, 58 pages**)**
Access:	2012: http://cdsco.nic.in/writereaddata/Bio%20Similar%20Guideline.pdf 2016: http://cdsco.nic.in/writereaddata/Proposed%20Guidelines%20for%20Similar%20Biologic%202016.pdf
Date:	**2012** 2016 (proposal)
Other:	**6. Principles for Development of Similar Biologic** Similar Biologic is developed through a sequential process to demonstrate the Similarity by extensive characterization studies revealing the molecular and quality attributes with regard to the Reference Biologic. Although the extent of testing of the Similar Biologic is likely to be less than that required for the Reference Biologic, it is essential that the testing of the Similar Biologic be sufficient to ensure that the product meets acceptable levels of safety, efficacy and quality to ensure public health in accordance with international guidelines. (WHO 2013).
Text:	2012: **8.5 Extrapolation of Efficacy and Safety Data to Other Indications** Extrapolation of the safety and efficacy data of a particular clinical indication (for which clinical studies has been done) of a similar biologic to other clinical indications may be possible if following conditions are met: • Similarity with respect to quality has been proven to reference biologic • Similarity with respect to preclinical assessment has been proven to reference biologic • Clinical safety and efficacy is proven in one indication • Mechanism of action is same for other clinical indications • Involved receptor(s) are same for other clinical indications New indication not mentioned by innovator will be covered by a separate application. 2016: **6. Principles for Development of Similar Biologics** …. In case the Reference Biologic is used for more than one indication, the Similar Biologic also qualifies for all the indications only if it is justified and if meets the conditions set forth in the section “Extrapolation of Efficacy and Safety Data to Other Indications”. Justification for extrapolation of indication shall be based on comparability in quality, preclinical and clinical studies, available literature data and whether or not the same mechanism of action is involved in specific indications. … **8.5 Extrapolation of Efficacy and Safety Data to Other Indications** Extrapolation of the safety and efficacy data of a particular clinical indication (for which clinical studies has been done) of a Similar Biologic to other clinical indications may be possible if following conditions are met: • Similarity with respect to quality has been proven to Reference Biologic • Similarity with respect to preclinical assessment has been proven to Reference Biologic • Clinical safety and efficacy is proven in one indication • Mechanism of action is same for other clinical indications • Involved receptor(s) are same for other clinical indications • However, new indications not mentioned by innovator will need to be covered by a separate application.

Region:	**USA (1)**
Title:	**Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Guidance for Industry;** April 2015 (Final), Biosimilarity Biosimilars**: Questions and Answers** Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; April 2015 (Final) Biosimilars: **Additional Questions and Answer**s Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, rev.1; May 2015 (Draft)
Access:	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf
Date:	**2015**
Text:	***4. Extrapolation of Clinical Data Across Indications*** If the proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the applicant may seek licensure of the proposed product **for one or more additional conditions of use for which the reference product is licensed.** However, the applicant would need to provide **sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought**. Such scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use: • The **MOA(s) in each condition of use** for which licensure is sought; this may include: – The target/receptor(s) for each relevant activity/function of the product – The binding, dose/concentration response, and pattern of molecular signaling upon engagement of target/receptor(s) – The relationships between product structure and target/receptor interactions – The location and expression of the target/receptor(s) • The **PK and bio-distribution** of the product in different patient populations (Relevant PD measures may also provide important information on the MOA.) • The i**mmunogenicity** of the product in different patient populations • Differences in **expected toxicities in each condition of use and patient population** (including whether expected toxicities are related to the pharmacological activity of the product or to off-target activities) • **Any other factor** that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought **Differences between conditions of use with respect to the factors described above do not necessarily preclude extrapolation. A scientific justification should address these differences in the context of the *totality of the evidence* supporting a demonstration of biosimilarity**. In choosing which condition of use to study that would permit subsequent extrapolation of clinical data to other conditions of use, FDA recommends that a sponsor consider **choosing a condition of use that would be adequately sensitive to detect clinically meaningful differences between the two products**. The sponsor of a proposed product may obtain licensure **only for a condition of use** that has been **previously licensed for the reference product**. If a reference product has a condition of use that was licensed under section 506(c) of the FD&C Act and 21 CFR part 601, subpart E (accelerated approval), and the reference product's clinical benefit in this condition of use has not yet been verified in postmarketing studies, the proposed product sponsor should consider studying another condition of use for which the reference product

Region:	USA (1)
	is licensed to avoid potential complications in the event that postmarketing studies fail to verify the clinical benefit of the reference product for the condition of use.
Q&A (Apr.15)	**Q. I.11.** Can an applicant extrapolate clinical data intended to support a demonstration of biosimilarity in one condition of use to support licensure of the proposed biosimilar product in one or more additional conditions of use for which the reference product is licensed? **A. I.11.** Yes. If the proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the applicant may seek licensure for one or more additional conditions of use for which the reference product is licensed. However, the applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.
Q&A Draft (May.15)	**Q. I.16. How can a proposed biosimilar product applicant fulfill the requirement for pediatric assessments under the Pediatric Research Equity Act (PREA)?**
Label	Separate Guidance

Region:	**USA (2)**
Title:	DRAFT**: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product;** Draft Guidance, Mai 2014 (Biosimilars)
Access:	http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf List: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm
Date:	**2014**
Text:	**II. The Role of Clinical Pharmacology Studies in the Demonstration of Biosimilarity** … clinical pharmacology studies often include PD endpoints (both therapeutic and toxic) and pharmacometric analysis to assess whether or not there are clinically meaningful differences between the proposed biosimilar and the reference product. If done well, they can add to the totality of the evidence, reduce residual uncertainty, and thus guide the need for and design of subsequent clinical testing to successfully support a demonstration of no clinically meaningful differences in the overall demonstration of biosimilarity. Clinical pharmacology data may be an **important component of the scientific justification supporting extrapolation of clinical data to one or more additional conditions of use**. The types of clinical pharmacology studies to be conducted will depend on the residual uncertainties about biosimilarity that these studies are capable of addressing in the context of the overall program for biosimilar product development.

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

Frankfurt am Main, den 8. Juni 2016