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International Pharmaceutical Regulators Forum

IPRF Biosimilars Working Group
Reflection Paper on Extrapolation of Indications in Authorization of Biosimilar Products

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1. Scope and Application

This reflection paper was prepared by the International Regulators Forum (IPRF) Biosimilars Working Group (BWG). Its purpose is to communicate the current thinking of various Regulatory Authorities of different regions with respect to the extrapolation of indications from the reference product to the biosimilar during the development of these products. This reflection paper is not legally binding and does not replace any local guidelines and regulations.

The Paper explores the issues associated with the use of extrapolation when authorizing biosimilar products for certain indications and proposes principles for the use of extrapolation in this context. The Paper also includes specific considerations for analytical, functional, and clinical evidence to support extrapolation of safety and efficacy information from the reference product to the biosimilar. However, this Paper does not deal with definitions of biosimilar terminology, regulatory requirements in demonstrating biosimilarity, or other issues which are subject to NRA-specific policies and procedures regulating biosimilar products.

Although decision-making is driven by scientific considerations in all jurisdictions, differences in legal or public health frameworks and clinical practices between countries can result in country-specific differences in which indications are authorized for a given biosimilar product. For example differences in expiry dates of patent or data protection between countries may result in authorization of an indication for a given biosimilar product in one country and not another.

2. Executive Summary

A stepwise approach is normally recommended throughout a biosimilar development program, starting with a comprehensive physicochemical and biological characterization. The extent and nature of the non-clinical *in vivo* studies and clinical studies to be performed depend on the level of evidence obtained in the previous step(s). The aim of the clinical studies is to confirm comparable clinical performance of the biosimilar and the reference (medicinal) product. Clinical studies may be designed to address residual uncertainty arising from differences observed in physicochemical comparisons, or properties thought not to be addressable through *in vitro* or nonclinical analyses.

The reference product may be authorized for more than one therapeutic indication. When similarity between the biosimilar and the reference product has been demonstrated based on the totality of the evidence generated from analytical, functional, non-clinical and clinical studies, indications may be authorized for the biosimilar even if clinical studies are not conducted in each indication. The demonstration of similarity established by the extensive side-by-side analytical, functional, non-clinical and clinical comparisons forms a scientific bridge between the biosimilar and the reference product that allows for the extrapolation of well-established safety and efficacy information from the reference product to the biosimilar. In designing a program to demonstrate similarity such that all indications of the reference product can be authorized, the clinical study population should be representative of the approved therapeutic indication(s) and be sensitive for ruling out potential differences in PK/PD, efficacy and safety endpoints between the biosimilar and the reference product.

Additional data are required where residual uncertainty remains which could impact on clinically meaningful differences between the biosimilar and the reference product.

3. Background

Extrapolation of data is already an established principle that has been exercised for many years in diverse scientific and regulatory contexts, e.g. in the case of major changes in the manufacturing process of originator products, the extrapolation of subcutaneous to intravenous use, and pediatric extrapolation. In the context of biosimilars, the majority of NRAs are in agreement with accepting the extrapolation of safety and efficacy information from the reference product to the biosimilar on the basis of the totality-of-evidence approach. However, there appears to be no clear consensus regarding what data should be submitted and how they should reach the conclusion to accept the extrapolation based on that evidence. Furthermore, the conclusions on the extrapolation can be different between NRAs based on legal, regulatory and/or scientific reasons, which may result in additional development requirements for the biosimilar industry.

Based on the comparison of the biosimilar guidelines released by several NRAs (Attachment 1), it appears that the regulators apply analogous biosimilar policies on the concept of extrapolation. In fact, there has been little variance in terms of regulatory decisions with regard to extrapolation decisions for individual products, with only a few exceptions (Attachment 2). Those guidelines are essentially the same in that if biosimilarity between a biosimilar product and the reference product has been demonstrated with appropriate scientific justification using the totality of evidence approach, the extrapolation of safety and efficacy information from the reference product to the biosimilar would be acceptable.

Most biosimilar guidelines address in common that the basis for extrapolation should come from an extensive analytical comparability exercise, including the characterization data, potency and/or *in vitro* assay(s) that cover the functionality of the molecule, and be supplemented by relevant clinical data. The mechanism(s) of action of the product and the pathophysiological mechanism(s) of the indicated diseases or conditions should be supported with published information on the reference product. The extrapolation of safety aspects including immunogenicity would require careful consideration because the immunogenicity could differ among indications in relation to concomitant medications-, patients- or disease-specific factors.

The objective of this Paper is to compile the common features of various biosimilar guidelines and to highlight to NRAs harmonized scientific considerations on extrapolation for biosimilar products, which would form the scientific basis for biosimilar product development and approval.

In order to improve efficiency of regulatory evaluation of biosimilars and support access to products of assured quality, safety and efficacy, it was recommended by the 16th International Conference of Drug Regulatory Authorities (ICDRA) that additional information on extrapolation should be added to the WHO guideline on similar biotherapeutic products.

4. General Considerations

4.1. Principles for Demonstrating Biosimilarity

The comparability exercise for demonstrating biosimilarity should be based on head-to-head comparisons of the proposed biosimilar and its reference product in terms of analytical,

non-clinical and clinical studies to demonstrate similarity in quality, safety and efficacy. When licensing a biosimilar product, all data generated during the comparability exercise should be considered, i.e. totality of evidence approach. Comparative quality assessments using state-of-the-art technology is the fundamental basis for demonstrating biosimilarity. Therefore, the comparability exercise should start from an extensive structural and functional characterization of the proposed biosimilar and its reference product in a comparative manner. It should focus on detecting analytical and biological (*in vitro*) differences between the proposed biosimilar and its reference product with sufficient sensitivity, and then move on to sequential *in vivo* similarity evaluations. In case differences are observed and, in order to tackle general remaining residual uncertainties, the associated concerns should be sufficiently addressed using sensitive models. This may be a progression from further *in vitro* data to sensitive clinical models based on PK/PD or clinical endpoints. In such a way, the totality-of-evidence approach should confirm the demonstration of biosimilarity.

The purpose of a clinical comparative study to demonstrate biosimilarity is not to independently (re)establish the safety and efficacy of the proposed biosimilar product but to support the evidence that the proposed biosimilar is highly similar to its reference product thereby providing confirmation there are no clinically meaningful differences between them.

4.2. Principles for Extrapolation of Indications

The major objective of extrapolation for biosimilar products is to avoid repeating unnecessary indication-specific clinical studies conducted previously during the development of the reference product. This principle is based on the sound scientific rationale that a repeat of the previous study or studies is not expected to provide additional information needed for the safe and effective use of the biosimilar product for the indication(s) of interest in place of the reference product. The accomplishment of this objective will also provide other benefits by reducing the quantity of clinical trial(s) needed for the approval of the biosimilar product. Hence, the principles of extrapolation should be consistent with this objective.

For extrapolation, the structural elements relevant to immunogenicity and to the mechanism(s) of action in the different indications are especially important. If there is a difference in a potentially functionally relevant attribute, it must be evaluated if this difference could have clinical consequences.

In general, if biosimilarity has been demonstrated based on analytical, functional, non-clinical and clinical studies, and appropriate justification is provided, indications for which the reference product is authorized may also be authorized for the biosimilar even if clinical comparative studies are not conducted in each indication. In other words, extrapolation of safety and efficacy information from the reference product to the biosimilar could be acceptable with appropriate scientific evidence and justification. Without conducting clinical comparative trial(s) in each indication held by the reference product, it is scientifically reasonable for an applicant to justify authorization of their biosimilar product in all or some approved indication(s) for the reference product.

Based on an analysis of biosimilar guidelines released by different NRAs to date (Attachment 1), the following factors should be taken into consideration for the justification of extrapolation:

- Whether the tested therapeutic indication is sufficiently sensitive for detecting the impact of potential differences in relevant aspects of efficacy and safety
- Whether the involved receptor(s) and/or clinically relevant mechanism(s) of action are the same. In this regard, detailed description of the scientific justification in terms of mechanism(s) of action and/or receptor(s) should be provided. If the receptor(s) and/or the mechanism(s) of action are different (or possibly unknown), a strong scientific rationale is necessary and additional data may be needed.
- In some guidelines, emphasis is placed on the mechanism(s) of the diseases (or conditions) involved and clinical experience with the reference product
- Any factors that may affect the safety profile including immunogenicity in each condition of use and in each patient population

The justification should be based on the totality of the evidence associated with analytical, non-clinical *in vitro* and *in vivo* (only where relevant) comparability studies, and clinical comparative studies. In addition to being sensitive and specific, the *in vitro* or *in vivo* non-clinical study should represent clinically relevant model to detect any differences between the proposed biosimilar and its reference product and support clinical study. The clinical study in this regard does not have to be a repeated confirmatory study as was conducted for the reference product but should be sufficiently sensitive to detect differences between the proposed biosimilar and its reference product. Otherwise, the applicant may conduct an additional clinical comparative study or studies in the indicated disease of interest.

Examples of the totality-of-evidence approach implemented successfully for the development of a sample of biosimilar products are summarized below as [annex 1].

5. Specific Considerations for the Extrapolation of Indications

When 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), a case can be made to extrapolate safety and efficacy findings from the reference product to the biosimilar product.

Additional data may be required in certain situations, such as

1. the active substance of the reference product interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indications
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 to detect the impact of potential differences in all relevant aspects of efficacy and safety

It is expected the applicant for the biosimilar product will discuss these requirements with the NRA.

5.1. Evidence from Analytical Comparability Study

Extrapolation may be justified on the basis that the proposed biosimilar and its reference product have highly similar structural, physicochemical, and biological attributes,

demonstrated using thorough state-of-the-art analytical and orthogonal methods with adequate sensitivity, specificity and validity. Highly similar, rather than the identical, quality attributes in this regard may mean that there could be some minor differences between the biosimilar and its reference product. Such difference(s) may trigger uncertainty regarding extrapolation. Therefore, the applicant should submit compelling evidence that any minor differences in quality attributes are not expected to produce different safety and efficacy outcomes in different indications between the two products as part of the scientific justification to support extrapolation.

In general, any minor differences in quality attributes should be identified in the early product development stage through the extensive physicochemical and functional characterization. Structural differences between a proposed biosimilar and its reference product are acceptable provided the variability in the heterogeneity pattern of the innovator molecule and reproducibility of analytical technology is suitably justified. However, any difference identified should be explained and justified with respect to the potential impact on the clinical efficacy and safety of the proposed biosimilar product.

An example of a minor difference in quality attributes is the increased level of phosphorylated high mannose-type structures seen in a biosimilar epoetin alfa in comparison to its reference product. In this case the applicant provided a justification that these are the common glycoforms of recombinant erythropoietins, and their presence is described in the literature for other recombinant cytokines and a large variety of non-lysosomal proteins from human plasma. They supplemented their application with additional *in vitro* data on mannose receptor binding which provided assurance that the level of high phosphorylated mannose type structures in the biosimilar did not impact on the efficacy or safety of the drug product. With an adequate explanation and justification, EMA accepted this difference had no impact on efficacy and safety, which could be extended to the overall consideration of extrapolation. (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000727/WC500020666.pdf)

The following summaries will explain the scientific support from the analytical comparability data for extrapolation granted for some recently licensed biosimilars.

- **Biosimilar erythropoietin**
  All licensed biosmilar epoetins exhibit the same amino-acid sequence as their reference products, and structural differences are confined to the microheterogeneous pattern of the molecule.

- **Biosimilar filgrastim**
  All licensed biosimilar filgrastims demonstrated a high level of similarity in molecular structure and biological activity with their reference products.

- **Biosimilar infliximab**
  Extensive analytical tests showed physicochemical and structural comparability except for a small difference in the proportion of afucosylated forms.

5.2. Evidence from *in vitro* and/or *in vivo* Functional Studies

The applicant should submit the *in vitro* assay results as an essential component supporting extrapolation on the basis that the biosimilar and its reference product have the same mechanism of action and biological activity. The assay methods should be of adequate

sensitivity, specificity and validity. *In vitro* studies may include, but are not limited to, biological assays, binding assays and enzyme kinetics. Examples are as follows:

- Assay for binding to target(s) (e.g., receptors, antigens, enzymes) known to be involved in the pharmacological and toxicological effects, and/or pharmacokinetics and pharmacodynamic characteristics of the reference product
- Assay for signal transduction and functional activity and/or viability of cells known to be of relevance for the pharmacological and toxicological effects of the reference product
- Fc functional assays; for monoclonal antibody products to predict a comparable cascade of immunological reactions and cytotoxicity in the potentially different pathophysiological settings of the indicated disease of interest

The applicant should discuss to what degree the *in vitro* studies used are representative and/or predictive for the clinical settings according to up-to-date scientific knowledge. If there are some differences in the *in vitro* results between the proposed biosimilar and its reference product, the applicant should provide justification or sufficient additional data and information that the observed differences are not expected to be clinically meaningful.

If the comparative analytical and non-clinical studies are considered satisfactory and no issues are identified that would preclude administration into humans, *in vivo* animal studies may not be necessary. If animal studies are required they should be performed where there is a clearly relevant species available to detect relevant differences and support extrapolation. It will also be important to choose reliably measurable effects such as changes in validated biomarker values and well-established pharmacological responses.

5.3. Evidence from Clinical Studies

Extrapolation may be supported on the basis that the biosimilar product has been demonstrated to be highly similar to its reference product after considering all of the comparative structural, functional, non-clinical and clinical data (even if clinical studies are not conducted in each therapeutic indication(s)) along with indication-specific justifications as described below. It should be noted that in certain situations, the combination of high analytical and non-clinical similarity combined with suitable human clinical PK/PD (where a clinically relevant PD marker exists) and immunogenicity studies may be sufficient to demonstrate biosimilarity. In such cases, the requirement for safety and efficacy studies may be waived.

The following conditions should be considered in the justification of extrapolation using clinical (efficacy and safety and/or PK+PD) data:

- Pharmacokinetic and pharmacodynamic data (where relevant markers exist) that show a high degree of similarity
- Clinical data showing highly similar efficacy profile between the proposed biosimilar and its reference product in sufficiently sensitive clinical setting
- Clinical data showing a comparable safety profile between the proposed biosimilar and its reference product in sufficiently sensitive clinical setting
- Differences in expected immunogenicity from the indication studied to the indication(s) to be extrapolated.

This should be justified considering the multiple factors including the route of administration, dosing regimen, patient-related factors, disease-related factors (e.g., co-medication, type of disease, immune status).

The following factors should be considered in the design of comparability studies for the justification of extrapolation using clinical data:

- Clinical trials for biosimilar products do not aim at demonstrating efficacy *per se*, since this has already been established with the reference product. The sole purpose of the clinical comparative study is to rule out differences that would be clinically significant. Therefore, it is essential for the applicant to perform the qualitative and quantitative evaluations of the similarity of the proposed biosimilar product to its reference product with sufficiently sensitive model of disease and measurement of sufficiently sensitive endpoint.
- With regards to safety data, justification may be needed because patient populations for different indications may have for instance, different comorbidities and may receive different concomitant medications. The applicant should determine the differences in expected safety determinants, if any, in each condition of use and patient population including whether the expected safety determinants are related to the pharmacological activity of the product or to off-target activities.
- Clinical experience with the reference product including the outcome of postmarketing surveillance, if publicly available.

The most crucial aspect to be considered for clinical evidence of comparability is the sensitivity of the studied indication and its relevance to the other indications. In order to extrapolate safety and efficacy information from the reference product to the biosimilar in each indication, the studied indication should be sufficiently sensitive to rule out any clinically meaningful differences in efficacy and safety (including immunogenicity) between the proposed biosimilar and its reference product. Consideration should be given to the sensitivity of the studied indication to the effects of the biosimilar and its reference product and the homogeneity of the study population. Thus, the applicant should justify that the studied indication is sensitive clinical model to support extrapolation.

The clinical data obtained from a well-controlled comparative study or studies would be very pertinent to dispel residual uncertainties remaining after physicochemical, structural and *in vitro* functional analyses. For this purpose, similarity margins should be pre-defined such that the study is sufficiently sensitive to discern clinically relevant differences.

Based on published regulatory reviews of approved biosimilar products (Attachments 3A and 3B), examples of sensitive clinical models suggested for the approval of a number of representative products with extrapolation are as follows:

- Biosimilar erythropoietin
  - Pharmacokinetic and pharmacodynamic comparison

  Healthy volunteers are the most sensitive population with fewer confounding clinical factors than patients when comparing pharmacokinetic and pharmacodynamic endpoints between the proposed biosimilar and reference product. Healthy volunteers are fully immunocompetent to assess the immunogenicity sensitively.

  - Clinical comparative study

The patients with renal anemia without major complications (e.g., severe and chronic infections or bleeding or aluminum toxicity) are expected to distinguish the potential differences between erythropoietin products on safety and efficacy reasonably well. The sensitivity to the effects of different erythropoietin products is greater in erythropoietin-deficient than non-erythropoietin deficient conditions and is also dependent on the responsiveness of the bone marrow. Patients with other causes of anemia may not be adequately sensitive for the biosimilar comparability exercise. For example, erythropoietin doses necessary to achieve or maintain target hemoglobin levels usually differ between pre-dialysis and dialysis patients. Those two populations should not be recruited in the same comparability study.

- Biosimilar filgrastim
  - Pharmacokinetic and pharmacodynamic comparison

  Healthy volunteers provide the most sensitive population to confirm a high level of similarity in the determination of pharmacokinetic and pharmacodynamic endpoints and to provide the evidence for the extrapolation of indications. The clinically relevant biomarkers (e.g., absolute neutrophil counts, CD34-positive cell counts) and the mechanism of action are consistent with patient populations. Their bone marrow is fully responsive to evaluate pharmacodynamic responses. There are much less clinical confounders in healthy volunteers than cancer patients. Healthy volunteers are also fully immunocompetent to assess the immunogenicity sensitively.

  - Clinical comparative study

  In efficacy and safety trials, patients receiving myelosuppressive chemotherapy are the most sensitive population for a comparability exercise. Cytotoxic chemotherapy is known to induce a severe neutropenia, the duration of which can be used as a clinical endpoint. If the pharmacodynamic response has been demonstrated using an appropriate model, clinical efficacy may not be required.

- Biosimilar somatropin
  - Pharmacokinetic comparison

  Healthy volunteers are the most sensitive population with fewer confounding clinical factors than patients when comparing pharmacokinetic endpoints between the proposed biosimilar and its reference product. Healthy volunteers are fully immunocompetent and sensitive to assess immunogenicity.

  - Clinical comparative study

  Children with growth hormone deficiency are more sensitive than those without growth hormone deficiency to determine the biosimilarity of somatropin products. The children with growth hormone deficiency are free from the interferences such as pubertal growth spurt.

- Biosimilar infliximab
  - Pharmacokinetic comparison

  Based on the review of the literature provided by the applicant, there is no evidence of notable differences in the PK of infliximab across its various indications. So patients with

rheumatoid arthritis or ankylosing spondylitis and healthy adults may also be seen as a sensitive population to determine the biosimilarity.

- Clinical comparative study

Patients with rheumatoid arthritis were considered a sensitive population to rule out any differences in efficacy and safety endpoints. Also, patients with ankylosing spondylitis appear to be a sensitive population to determine biosimilarity and to obtain appropriate data for the extrapolation of indications.

Patients with an inadequate response to methotrexate treatment have a larger effect size (infliximab *versus* placebo) for the comparison of infliximab efficacy than patients treated using the first line therapy including methotrexate.

The sensitive models could not only be related to products as described above but also to the route of administration. If the reference product can be administered intravenously and subcutaneously, and if both routes are applicable to comparability exercise, it is preferable to investigate both routes of administration. However, as the evaluation of subcutaneous administration covers both absorption and elimination phases, the evaluation of intravenous administration may be omitted if the similarity in both absorption and elimination phases has been demonstrated for the subcutaneous route using additional pharmacokinetic parameters such as the partial area under the concentration-time curves. In any case, the applicant will still need to provide the justification as such.

When application for product authorization is submitted, the immunogenicity data obtained up to the completion of efficacy studies should be provided and, if available, additional follow-up data should be submitted. Since pre-authorization immunogenicity data are often limited, further characterization of the immunogenicity profile is usually necessary in the post-marketing stage, particularly if rare antibody-related serious adverse events may occur that are not likely to be detected in the pre-marketing phase.

The most sensitive model may not be available for the development of all biosimilar products. In such circumstances, the applicant should make an effort to establish alternative models through discussion / advice with the NRA.

The correlation between the ‘firm’ clinical endpoints recommended by the guidelines for new active substances and other clinical or pharmacodynamic endpoints may have been demonstrated in previous clinical trials with the reference product. The same primary efficacy endpoints as those that were used in the marketing authorization application of the reference product may be used because a large body of historical data is generally available in the public domain for setting the equivalence margin and calculating the sample size. On the other hand, the study endpoints may be different from those that were used in the marketing authorization application of the reference products, as more sensitive endpoints may exist for detecting clinically meaningful differences. The applicant is encouraged to discuss with each NRA when designing the clinical trial.

5.4. Evidence from Publicly Available Information

Publicly available information should be used to support the scientific principles associated with extrapolation. In these cases, the applicant can submit the publicly available information such as regulatory reviews and research articles as supporting materials. The review should be

the formal document that contains the scientific and regulatory information on the determination of biosimilarity that the NRAs participating in the IPRF have released for the public. The research article should include reliable scientific information and have been published in a widely-recognized scientific journal. It is recommended that the applicant should provide a critical analysis of public scientific information. Such cases include but are not limited to:

- Mechanism(s) of action and/or receptor-level interactions involved for the indication(s) of interest to be extrapolated
- If the mechanism of action is not known, the applicant may provide their justification on the mechanism with a scientific basis published in the reliable literature. It needs a comprehensive discussion of the available literature including the involved receptor(s) and the hypothesized mechanism(s) of action.
- Similarity in pathophysiological mechanism(s) between the indications studied in a clinical trial(s) and intended to be extrapolated

5.5. Evidence to be provided where a Residual Uncertainty Remains

For indication where residual uncertainty precludes the extrapolation of safety and efficacy information from the reference product to the biosimilar, additional clinical data will be required. The applicant for the biosimilar product is expected to discuss these requirements with the NRA.

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Attachments

1. Gap Analyses for Biosimilar Guidelines on the Extrapolation of Indications (as of Jun. 2015)
2. Biosimilar Products Approved with Extrapolated Indications (as of Jun. 2015)

3A. Selected Summary of Regulatory Biosimilar Reviews by Year (as of Jun. 2015)

- Erythropoetin, Filgrastim, Somatropin, Infliximab, Insulin

3B. Selected Summary of Regulatory Biosimilar Reviews by Agent (as of Jun. 2015)

- Erythropoetin, Filgrastim, Infliximab

[Annex 1] Example of the totality-of-evidence approach (as of Jun. 2015)

- Biosimilar filgrastim

Biosimilar filgrastim was approved for the treatment of neutropenia of various etiologies and for the mobilization of peripheral blood progenitor cells in patients and healthy donors, respectively. All indications of the reference product have been approved for the proposed biosimilar product. The *in vitro* data collected from several analytical tests demonstrated that the molecular structure, receptor binding and biological activity was comparable between the proposed biosimilar and its reference product of filgrastim. The clinical PK/PD study conducted in healthy subjects for the purpose of the comparability exercise indicates that the pharmacokinetic, pharmacodynamic, safety (including immunogenicity) profiles are also highly similar. Such a totality-of-evidence approach supports the extrapolation of all indications for the biosimilar filgrastim.

- Biosimilar erythropoietin

Biosimilar erythropoietin was approved for the treatment of anemia associated with chronic renal failure or induced by chemotherapy, to increase the yield of pre-operative autologous blood, and to reduce exposure to allogenic blood transfusions prior to surgery. The extrapolation from the reference product to the biosimilar has been based on the totality of the evidence demonstrating biosimilarity. The supporting data demonstrate comparability in physicochemical and functional properties, the same mechanism of action in all approved indications, the highly similar effects on reticulocyte counts and hemoglobin values that gives reassurance to the efficacy profiles in a clinical study, and the similar safety profiles including anti-erythropoietin antibody production.

- Biosimilar infliximab

Biosimilar infliximab was authorized for all proposed indications (except for inflammatory bowel disease as its reference product, Remicade in Canada). The extrapolation of indications was fulfilled based on the consideration of the totality of the evidence derived from the comparability exercise in terms of physicochemical and structural properties, mechanism of action, pharmacokinetic and pharmacodynamic evaluations, and safety and efficacy profiles assessed in the treatment of rheumatoid arthritis in a clinical study. The totality of evidence is deemed to support the similar efficacy and safety profiles between biosimilar infliximab and Remicade for all approved indications of Remicade from the cluster of rheumatic disease and psoriasis. For inflammatory bowel disease, however, this has not been unequivocally accepted by all NRAs.

As implied in the examples, it is important to clearly link the *in vitro* comparability results to demonstrating that there would be no clinically meaningful differences between the proposed biosimilar and its reference product. For example, understanding the mechanism of action in different indications is one of the major issues in the extrapolation of indication(s). Whereas EMA, MFDS and PMDA granted the extrapolation of all Remicade indications[1] for the approval of biosimilar infliximab (Remsima, Celltrion), Health Canada initially excluded inflammatory bowel diseases in the extrapolation and required additional data from the

[1] In Japan and Korea, according to their guideline, indications where re-examination periods were expired have been approved.

applicant before authorizing the biosimilar for all indications later. The US FDA also granted the extrapolation of all Remicade indications[2] for the approval of biosimilar infliximab (Inflectra, Celltrion). [3]

Although it is not always possible to compare the pharmacokinetic, pharmacodynamic and clinical profiles by observing the direct action of the proposed biosimilar and its reference product without any interference from concomitant medication, it would be more desirable for the applicant to obtain biosimilarity data in an unconfounded setting to strengthen support for extrapolation.

[2] In their reviews, FDA noted that Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. Accordingly, FDA will not license CT-P13 for this indication until the orphan drug exclusivity expires.

[3] FDA did not authorize the Celltrion product in the first review cycle and requested additional data to support, in part, that the products were analytically highly similar.

[SUMMARY TABLE] Gap Analysis of Biosimilar Guidelines for the Extrapolation of Indications

	EMA	FDA	Health Canada	MFDS	PMDA	WHO
Pre-requisites	Overall evidence of comparability data (i.e., quality, non-clinical and clinical safety/efficacy data) with adequate justification in one indication	Data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use	Proposals for additional indications held by the reference biologic drug may be granted to the SEB in the absence of such clinical data, if rationales are sufficiently persuasive	Similar efficacy and safety of the biosimilar product and the reference have been demonstrated for a particular clinical indication	Efficacy and pharmacological effects of the follow-on biologic have been demonstrated to be comparable to one of the indications of the original biologic	Efficacy and safety of the SBP and RBP have been demonstrated for a particular clinical indication
Required Basis Data	- Thorough physicochemical and structural analyses data; - In vitro functional tests data; - Clinical data (efficacy and safety and/or PK/PD) in one indication	- MOA(s) in each condition of use; - PK and bio-distribution, PD measures(if feasible); - Immunogenicity; - Expected toxicities; - Any other factor that may affect safety/effectiveness Differences between conditions of use with respect to the above factors should be justified in the context of the totality of the evidence supporting biosimilarity.	- MOA(s) and pathophysiological mechanism(s); - Safety profile in the respective conditions and/or populations; and - Clinical experience with the reference 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.	- Sensitive clinical test model - Clinically relevant MOA and/or involved receptor(s) - Safety, immunogenicity	- Efficacy and pharmacological effects - MOA or the mechanism of each indication	- Sensitive clinical test model - Clinically relevant MOA and/or involved receptor(s) - Safety and immunogenicity
Clinical Test Model	Relevant and sensitive for the others in terms of efficacy or safety (if not sensitive for differences in all relevant aspects of efficacy and safety, additional data are required).	The most sensitive one to detect clinically meaningful differences in safety (including immunogenicity) and effectiveness.	Select population allow to detect of significant differences between the SEB and the reference biologic drug.	Sensitive clinical test model that is able to detect potential differences between the biosimilar product and the reference product.		A sensitive clinical test model that is able to detect potential differences between the SBP and the RBP.

[SUMMARY TABLE] Gap Analysis of Biosimilar Guidelines for the Extrapolation of Indications (continued)

	EMA	FDA	Health Canada	MFDS	PMDA	WHO
MOA(s)	- Mode of action of the active substance (receptor(s) involved) in all the authorised indications of the reference product need to be considered - Pathogenic mechanisms involved in the disorders included in the therapeutic indications (e.g. mechanisms shared by various therapeutic indications) need to be considered Additional clinical data are required if active substance of the reference product interacts with several receptors that may have a different impact in the tested and non-tested indications or itself has more than one active site and the sites may have a different impact in different indications.	The MOA(s) in each condition of use for which licensure is sought; this may include: - Target/receptor(s) for each relevant activity/function - Binding, dose/concentration response, molecular signaling upon engagement of target/receptor(s) - Relationship between product structure and target/receptor interactions - Location and expression of the target/receptor(s)	- Mechanism(s) of action need to be considered - Pathophysiological mechanism(s) of the disease(s) or conditions involved need to be considered	Additional clinical data are required in certain situations if reference product interacts with different receptors (or active sites) that may have a different impacts on the tested and non-tested indications.	A different MOA or the mechanism of each indication remains unclear, the comparability of efficacy with the original biologic should be demonstrated for each indication, without extrapolation.	If the MOA is different or not known, a strong scientific rationale and additional data (e.g., “PD fingerprint”, additional clinical data) will be needed.
Extra-polation of safety	Requires careful consideration with route of administration, dosing regimen, patient-related factors, and disease-related factors.	Should be cautious with comorbidities and concomitant medications across indications.	The immunogenicity of the SEB should be evaluated using appropriately designed clinical studies with state-of-the-art methods, taking into consideration the potential impact on both the efficacy and the safety.	Consider comedications, comorbidities and immune status of patient populations; reactions related to target cells (e.g. tumor cell lysis) of diseases.		Sufficiently characterized safety and immunogenicity of the SBP and no unique/additional safety issues expected for the extrapolated indication(s).

Attachment 1. Gap Analysis of Biosimilar Guidelines for the Extrapolation of Indications

Gap Analysis of Biosimilar Guidelines for the Extrapolation of Indications

	Regulatory Considerations	Required Basis Data for Extrapolation	Additional Necessary Considerations
EMA	■ Extrapolation of clinical data to other indications could be acceptable when biosimilar comparability has been demonstrated in one indication ■ **Based on the overall evidence of comparability** provided from the comparability exercise and with adequate justification	■ Extrapolation should be considered in the light of the totality of data (i.e., quality, non-clinical and clinical data) ○ **Thorough Physicochemical and structural analyses data** ○ **In vitro functional tests data** ○ **Clinical data in one therapeutic indication** - **Efficacy study data** - **And safety study data** - **And/or PK&PD study data** ■ **Extrapolation of safety including immunogenicity** data also requires careful consideration ○ From the studied indication/route of administration to other uses of the reference product should be justified ○ Immunogenicity could differ among indications - Related to multiple factors including the route of administration, dosing regimen, patient-related factors, disease-related factors (e.g., co-medication, type of disease, immune status)	■ Additional data are required in certain situations, such as: ○ Active substance of the reference product **interacts with several receptors that may have a different impact** in the tested and non-tested therapeutic indications ○ Active substance itself has **more than one active site and the sites may have a different impact** in different therapeutic indications ○ Studied therapeutic indication is not relevant for the others in terms of efficacy or safety (i.e., **not sensitive for differences in all relevant aspects of efficacy and safety)** ■ If pivotal evidence for comparability is based on PD and for the claimed indications different MOA are relevant (or uncertainty exists), then applicants should provide relevant data to support extrapolation to all claimed clinical indications ○ Support such extrapolations **with a comprehensive discussion of available literature** including the involved receptor(s) and mechanism(s) of action
FDA	■ If data from a **clinical study sufficient to demonstrate safety, purity, and potency** in an appropriate condition of use, the potential exists for the proposed product to be licensed for one or more additional conditions of use	Scientific justification should address the following issues for the tested and extrapolated conditions of use: ■ **MOA(s) in each condition of use** for which licensure is sought; including: ○ Target/receptor(s) for each relevant activity/function of the product ○ Binding, dose/concentration response, and pattern of molecular signaling upon engagement of target/receptor(s) ○ Relationship between product structure and target/receptor interactions ○ Location and expression of the target/receptor(s) ■ **PK and bio-distribution** of the product in different patient populations; PD measures may provide important information on the MOA ■ 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)	■ In choosing which condition of use to study that would permit subsequent extrapolation of clinical data to other conditions of use, a sponsor consider **whether the tested condition of use is the most sensitive one** to detect clinically meaningful **differences in safety (including immunogenicity) and effectiveness** ■ A sponsor should be cautious with respect to the extrapolation of **safety risk profiles across indications** because patient populations for different indications may have different **comorbidities** and may receive different **concomitant medications**

		■ Any other factor that may affect the **safety or effectiveness** of the product in each condition of use and patient population A scientific justification should address the differences between conditions of use with respect to the above factors in the context of the totality of the evidence supporting a demonstration of biosimilarity.	
Health Canada	■ Proposals for additional indications held by the reference biologic drug may be granted to the SEB in the absence of such clinical data ■ In some cases, **comparative PK&PD data** to bridge 2 or more indications **may be sufficient**	■ 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** should be provided to adequately support the data extrapolation
MFDS	■ If similar efficacy and safety of the biosimilar product and the reference product have been demonstrated for a particular clinical indication, extrapolation of these data to other indications for which post-marketing survey was completed may be possible	■ **All of the following conditions should be fulfilled**: ○ **Sensitive clinical test model** that is able to detect potential differences between the biosimilar product and the reference product ○ **Clinically relevant MOA and/or involved receptor(s) are the same** ○ **Safety and immunogenicity** have been sufficiently characterized ■ Other than the above conditions for extrapolation of therapeutic indications for biosimilar products, extrapolation should be considered in the light of the totality of evidence, which is the overall evidence of comparability data and potential uncertainties.	■ Additional data are required in certain situations, such as: ○ Reference product **interacts with different receptors (or active sites) that may have a different impacts** on the tested and non-tested indications ○ **Safety profiles** across therapeutic indications have a difference ■ For safety extrapolation, consider the following factors: ○ **Comedications, comorbidities and immune status** of patient populations ○ **Reactions related to target cells**(e.g. tumor cell lysis) of diseases
PMDA	■ Possible to extrapolate from one approved indication to the other approved indications	■ 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, comparability of pharmacological effects on the other indications can be expected ■ However, where each relevant indication have **a different MOA or the mechanism of each indication remains unclear,** the comparability of efficacy with the original biologic should be demonstrated for each indication, **without extrapolation**	

WHO	■ 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 may be possible	■ **All of the following conditions are fulfilled**: ○ **A sensitive clinical test model** that is able to detect potential differences between the SBP and the RBP ○ The clinically relevant **MOA and/or involved receptor(s) are the same** ○ **Safety and immunogenicity** of the SBP have been sufficiently characterized and there are **no unique/additional safety issues expected** for the extrapolated indication(s)	■ If the MOA is **different or not known,** a strong scientific rationale and **additional data** (e.g., "PD fingerprint", additional clinical data) **will be needed** ■ 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 ■ 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

■ **Abbreviations:**

PK, Pharmacokinetic; PD, Pharmacodynamics; MOA, Mechanism of action; SBP, Similar Biotherapeutic Product; SEB, Subsequent Entry Biologics; RBP, Reference Biotherapeutic Product; GH, Growth Hormone

■ **References:**

EMA
Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (2014)

FDA
GUIDANCE FOR INDUSTRY: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (2015)

Health Canada
GUIDANCE FOR SPONSORS: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) (2010)

MFDS
Guidelines on the Evaluation of Biosimilar Products, English version, Revision 1 (2015)

PMDA
Guideline for the Quality, Safety, and Efficacy Assurance of Follow-on Biologics (2009)

WHO
Guidelines on evaluation of similar biotherapeutic products (SBPs) (2009)

Attachment 2. Biosimilar Products Approved with Extrapolated Indications

ERYTHROPOIETIN					
Agency	**Reference**		**Agency**	**Biosimilar**	
	EMA	**PMDA**		**EMA**	**PMDA**
Product Name (Applicant)	Eprex/Erypo, Epoetin alfa (Janssen-Cilag GmbH)	ESPO, Epoetin alfa (Kyowa Hakko Kirin)	**Product Name (Applicant)**	Abseamed (Medice Arzneimittel Pütter) Binocrit (Sandoz) Epoetin alfa hexal (Hexal) Retacrit (Hospira) Silapo (Stada)	Epoetin alfa BS (JCR Pharmaceuticals)
Approved Indications	■ Anemia in CRF patient ○ Adult on HD ■ Anemia in CRF patient ○ Pediatric on HD ○ Adult on PD ○ Adult not yet on dialysis ■ Chemotherapy-induced anaemia in adult cancer patient ■ Increase the yield of PAD ■ Reduction of need for allogenic blood transfusions in adult prior to surgery	■ Renal anemia undergoing HD ■ Renal anemia undergoing PD ■ Anemia of prematurity	***Tested Model**	■ Anemia in CRF patient ○ Adult on HD	■ Renal anemia undergoing HD
			Extrapolated Indications	■ Anemia in CRF patient ○ Pediatric on HD ○ Adult on PD ○ Adult not yet on dialysis ■ Chemotherapy-induced anemia in adult cancer patient ■ Increase the yield of PAD ■ Reduction of need for allogenic blood transfusions in adult prior to surgery[1]	■ Renal anemia undergoing PD ■ Anemia of prematurity

* Tested in the clinical efficacy and safety study

[1]Indications added in 2010

Abbreviations
CRF, chronic renal failure; HD, hemodialysis; PD, peritoneal dialysis; PAD, pre-operative autologous blood of donation

Attachment 2. Biosimilar Products Approved with Extrapolated Indications

<table>
<tr><th colspan="5">FILGRASTIM</th></tr>
<tr><th rowspan="2">Agency</th><th colspan="3">Reference</th><th rowspan="2">Agency</th><th colspan="3">Biosimilar</th></tr>
<tr><th>EMA</th><th>FDA</th><th>PMDA</th><th>EMA</th><th>FDA</th><th>PMDA</th></tr>
<tr><td>Product Name (Applicant)</td><td>Neupogen (Amgen)</td><td>Neupogen (Amgen)</td><td>Gran (Kyowa Hakko Kirin)</td><td>Product Name (Applicant)</td><td>Biograstim (CT Arzneimittel)
Ratiograstim (Ratiopharm)
Tevagrastim (Teva)
Zarzio (Sandoz)
Filgrastim Hexal (Hexal AG)
Nivestim (Hospira)
Accofil (Accord Healthcare)
Grastofil (Apotex)</td><td>Zarxio (Sandoz)</td><td>Filgrastim BS (Fuji Pharma),(Mochida)

Filgrastim BS (Teva Pharma Japan)
Filgrastim BS (Sandoz)</td></tr>
<tr><td rowspan="3">Approved Indications</td><td colspan="3">■ Patients with nonmyeloid malignancies receiving myelosuppressive CTX

■ Patients with Acute Myeloid Leukemia
■ Cancer patients receiving myeloablative CTX followed by bone marrow transplantation
■ Cancer patients receiving PBPC collection & therapy
■ Severe congenital, cyclic, or idiopathic neutropenia
■ Patients with HIV infection</td><td>*Tested Model</td><td colspan="3">■ Patients with nonmyeloid malignancies receiving myelosuppressive CTX</td></tr>
<tr><td colspan="3" rowspan="2">■ Neutropenia associated with myelodysplastic syndromes or aplastic anemia</td><td rowspan="2">Extrapolated Indications</td><td colspan="2">■ Patients with Acute Myeloid Leukemia
■ Cancer patients receiving myeloablative CTX followed by bone marrow transplantation
■ Cancer patients receiving PBPC collection & therapy
■ Severe congenital, cyclic, or idiopathic neutropenia
■ Patients with HIV infection</td><td></td></tr>
<tr><td colspan="2"></td><td>■ Neutropenia associated with myelodysplastic syndromes or aplastic anemia</td></tr>
</table>

* Tested in the clinical efficacy and safety study

Abbreviations

CTX, chemotherapy; HIV, human immunodeficiency virus; PBPC, peripheral blood progenitor cells

Attachment 2. Biosimilar Products Approved with Extrapolated Indications

INFLIXIMAB							
Agency	**Reference Drug**		**Agency**	**Biosimilar**			
	PMDA	**All the Other**		**MFDS**	**EMA**	**Health Canada**	**PMDA**
Product Name (Applicant)	Remicade (Janssen Biotech)		**Product Name (Applicant)**	Remsima (Celltrion)	Remsima (Celltrion) Inflectra (Hospira)	Remsima (Celltrion) Inflectra (Hospira)	Infliximab BS (Celltrion/Nippon Kayaku)
Approved Indications	■ AS ■ RA ■ CD ■ UC ■ Psoriatic Arthritis ■ Psoriasis ■ Behcet's Uveitis	■ AS ■ RA ■ Adult CD ■ Pediatric CD ■ Adult UC ■ Paediatric UC ■ Psoriatic arthritis ■ Psoriasis	**Tested Model**	■ AS[1] ■ RA[2]		■ RA	
			Extrapolated Indications	■ Adult CD ■ Pediatric CD[3] ■ Adult UC ■ Pediatric UC[3] ■ Psoriatic arthritis ■ Psoriasis	■ Adult CD ■ Pediatric CD ■ Adult UC ■ Pediatric UC ■ Psoriatic arthritis ■ Psoriasis	■ Psoriatic arthritis ■ Psoriasis	■ CD ■ UC

[1] Pivotal pharmacokinetic and supportive clinical efficacy and safety study
[2] Pivotal clinical efficacy and safety and supportive pharmacokinetic study
[3] Indications added in 2015

Notes

The extrapolated indications of infliximab vary by agencies, which is mainly based on the interpretation discrepancies about different *in vitro* ADCC activities.

- MFDS: *Not mentioned*
- EMA: The difference detected has no clinically relevant impact on the efficacy and safety, in particular in IBD.
- Health Canada: While ADCC is not an important mechanism in psoriatic arthritis and psoriasis, it cannot be ruled out as a mechanism of action in IBD and the differences in ADCC activities could have an impact on the clinical safety and efficacy in IBD.
- PMDA: The reference drug and its biosimilar have comparable biological activities, efficacy and safety and are considered to have similar pharmacological activities based on the fact that RA, CD and UC share a common pathologic mechanism and infliximab's mechanism of action. (*Not mentioned about psoriatic diseases.*)

Abbreviations

ADCC, antibody-dependent cell-mediated cytotoxicity; AS, ankylosing spondylitis; CD, Crohn's disease; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; UC, ulcerative colitis

Attachment 2. Biosimilar Products Approved with Extrapolated Indications

SOMATROPIN								
Agency	**Reference Drug**			**Agency**	**Biosimilar**			
	EMA PMDA	**MFDS**	**Health Canada**		**PMDA**	**Health Canada**	**EMA**	**MFDS**
Product Name (Applicant)	Genotropin (Pfizer)			**Product Name (Applicant)**	Somatropin BS (Sandoz)	Omnitrope (Sandoz)		Scitropin (SciGen Korea)
Approved Indications	■ GHD in pediatric	■ GHD in pediatric	■ GHD in pediatric	***Tested Model**	■ GHD in pediatric			
	■ GHD in adult ■ PWS ■ SGA ■ TS ■ Growth Disturbance in CRF	■ GHD in adult ■ PWS ■ SGA ■ TS ■ Growth Disturbance in CRF ■ ISS[1]	■ GHD in adult ■ SGA[2] ■ TS[2] ■ ISS[2]	**Extrapolated Indications**	■ GHD in adult ■ PWS[2] ■ SGA[2] ■ TS ■ Growth Disturbance in CRF	■ GHD in adult ■ SGA[3] ■ TS[3] ■ ISS[3]	■ GHD in adult ■ PWS ■ SGA ■ TS ■ Growth Disturbance in CRF	■ GHD in adult ■ PWS ■ SGA ■ TS ■ Growth Disturbance in CRF ■ ISS

* Tested in the clinical efficacy and safety study

[1]Indications added in 2009
[2]Indications added in 2013
[3]Indications added in 2014

Abbreviations
CRF, chronic renal failure; GHD, growth hormone deficiency; ISS, idiopathic short stature; PWS, Prader-Willi syndrome; SGA, small for gestational age; TS, Turner syndrome

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64 **[Table] Approved Biosimilars**

Drug	Approval Agency				
	EMA	**FDA**	**HEALTH CANADA**	**PMDA**	**MFDS**
Erythropoietin	■ Abseamed (2007) ■ Binocrit (2007) ■ Epoetin alfa hexal (2007) ■ Retacrit (2007) ■ Silapo (2007)			■ Epoetin alfa BS (2010)	
Filgrastim	■ Tevasgrastim (2008) ■ Ratiograstim (2008) ■ Biograstim (2008) ■ Zarzio (2009) ■ Filgrastim hexal (2009) ■ Nivestim (2010) ■ Accofil (2014) ■ Grastofil (2014)	■ Zarxio (2015)		■ FilgrastimBS (Fuji, 2012) ■ FilgrastimBS (Teva, 2013) ■ FilgrastimBS (Sandoz, 2014)	
Somatropin	■ Omnitrope (2006)		■ Omnitrope (2009)	■ Somatropin BS (2009)	■ SciTropin A (2014)
Insulin	■ Abasaglar (2014)			■ Insulin glargine BS (2015)	
Infliximab	■ Remsima (2013) ■ Inflectra (2014)		■ Inflectra (2014) ■ Remsima (2014)	■ Infliximab BS (2014)	■ Remsima (2012)
Trastuzumab					■ Herzuma (2014)
Etanercept					■ Davigtrel (2014)

Attachment 3A. Selected Summary of Regulatory Biosimilar Reviews by Year

ERYTHROPOIETIN ① **Clinical Pharmacokinetic / Pharmacodynamic Studies**			
Approved Year (Agency)	**2007 (EMA)**	**2007 (EMA)**	**2010 (PMDA)**
Products Name	**Abseamed, Binocrit, Epoetin alfa Hexal**	**Retacrit, Silapo**	**Epoetin Alfa BS Injection [JCR]**
Reference Products	**Eprex/Erypo**		**ESPO, Epoetin alfa**
Study Type	**5 PK, PD studies (1 pilot study, 2 pivotal studies)**	**2 PK studies**	**3 PK studies**
Primary + Secondary Objective	Equivalence in PK + PD	Equivalence in PK + Safety	Equivalence in PK + Safety
Study Subjects	Healthy adult male	Healthy adults	Healthy male HD patients with renal anemia Healthy
Study Design	Randomised, 2-centre, open**, parallel-group** - Multiple IV 100 IU/kg TIW Randomized, monocentric, open, **parallel-group** - Multiple SC 100 IU/kg TIW	**2-period cross-over** - Single-dose IV bolus injection **3-period cross-over** - Single-dose SC bolus injection	Exploratory, placebo-controlled, single-center, **parallel-group** - **S**ingle-dose IV injection **2-period cross-over** - Single-dose IV injection **2-period cross-over** - Single-dose SC injection
Primary Endpoint	***[PK]*** AUCτ of EPO	***[PK]*** $AUC_{0\text{-tlast}}$	***[PK]*** $AUC_{0\text{-}\infty}$ (IV), $AUC_{0\text{-}\infty,}$ & Cmax (SC)
	[PD] Absolute Hgb response (AUEC)	***[PD]*** Reticulocyte count	***[PD]*** N/A
Equivalence Margin	**post hoc acceptance range of 80-125%**	**post hoc acceptance range of 80-125% for AUC & 70-143% for Cmax**	
NOTE	- Two of the PK/PD studies irrelevant to comparability exercise - No pre-defined equivalence margin	- No specific PD studies conducted with SB309. The PD of erythropoietin is known and described in the literatures. - No pre-defined equivalence margin	- No specific clinical PD study conducted with JR-013

Abbreviation: AUC, area under the concentration-time curve; AUEC, area under the effect curve; Cmax, maximum serum concentration; EPO, erythropoietin; HD, hemodialysis; IV, intravenous; N/A, not available; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous

Attachment 3A. Selected Summary of Regulatory Biosimilar Reviews by Year

ERYTHROPOIETIN ② Clinical Efficacy / Safety Studies			
Approved Year (Agency)	**2007 (EMA)**	**2007 (EMA)**	**2010 (PMDA)**
Products Name	**Abseamed, Binocrit, Epoetin alfa Hexal**	**Retacrit, Silapo**	**Epoetin Alfa BS Injection [JCR]**
Reference Products	**Eprex/Erypo**		**ESPO, Epoetin alfa**
Study Type	**1 pivotal comparative study,** **1 supportive non-comparative study**	**2 pivotal comparative study,** **2 supportive, uncontrolled safety study** ****1 additional comparative SC study (2009) for Retacrit® only**	**1 phase 2/3 comparative IV study,** **1 long-term non-comparative IV study**
Primary, Secondary Objective	Therapeutic equivalence in efficacy + safety	Therapeutic equivalence in efficacy + safety	Therapeutic equivalence in efficacy + safety
Study Subjects	Renal anemia on HD	Renal anemia on HD	Renal anemia on HD
Study Design	Randomised, double blind, multicenter, **parallel-group** - IV	[Correction phase IV study] Randomized, double-blind, multi-center, verum-controlled, **parallel-group** - Multiple-dose IV [Maintenance phase IV study] Randomized, double-blind, multi-national, verum-controlled, **cross-over** - Multiple-dose IV **[Additional maintenance phase SC study] Randomized, double-blind, multi-national, multiple-dose SC, **parallel-group**	Randomized, double-blind, multi-center, **parallel-group** - Multiple-dose IV
Primary Endpoint	***[Efficacy]*** Mean absolute change in Hgb levels between the screening/baseline period and the evaluation period ***[Safety]*** Incidence of adverse events, serious adverse event, treatment-emergent adverse events, death, physical exam, clinical lab tests	***[Efficacy]*** [Correction phase IV study] - Mean Hgb levels during the last four -weeks of treatment - Mean weekly dosage of EPO per kg body weight during the last four weeks of treatment [Maintenance phase IV study] - Intra-individual change (test-reference) in mean weekly dosage per kg body weight of each product during the double-blind treatment period - Intra-individual change (test-reference) in mean Hgb level during double-blind treatment with each study drug	***[Efficacy]*** Absolute change in Hgb levels between the screening/baseline period and the evaluation period ***[Safety]*** Not applicable

		[Maintenance phase SC study] - Mean Hgb levels during the last four -weeks of treatment - Mean weekly dosage of EPO per kg body weight during the last 4 weeks of treatment *[Safety]*** Occurrence of anti-EPO antibodies, incidence of Hgb levels above 13 g/dl, ratings of tolerability, evaluation of adverse events	
Statistics	Equivalence	Equivalence	Equivalence
Equivalence Margin	- Equivalence margin of ± 0.5 g/dl in Hgb (mean baseline Hgb = < 11.5 and > 11/5 g/dl)	[Correction phase IV study] - 95% CI of the difference between both treatment groups of the primary endpoints - Equivalence margin of ± 1 g/dl in Hgb and ± 45 IU/kg/week (*corrected from 14 IU/kg/week) for mean weekly EPO dosage [Maintenance phase IV study] - 2-sided 95% CI of the intra-individual change (test-reference) - Equivalence margin of ± 0.6 g/dl in Hgb and ± 14 IU/kg/week for mean weekly EPO dosage [Maintenance phase SC study] - 95% CI of the difference between both treatment groups of the primary endpoints - Equivalence margin of ± 0.5 g/dl in Hgb and ± 45 IU/kg/week for EPO dosage	- 95% CI - Equivalence margin of ± 0.5 g/dl in Hgb
NOTE	- Pre-defined acceptance ranges for equivalence margin	- Pre-defined acceptance ranges for equivalence margin	- Pre-defined acceptance ranges for equivalence margin

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; EPO, erythropoietin; Hgb, hemoglobin; HD, hemodialysis; IU, international unit; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous

Attachment 3A. Selected Summary of Regulatory Biosimilar Reviews by Year

FILGRASTIM ① **Clinical Pharmacokinetic / Pharmacodynamic Studies***							
Approved Year (Agency)	**2008 (EMA)**	**2009 (EMA)**	**2010 (EMA)**	**2012 (PMDA)**	**2013 (PMDA)**	**2014 (EMA)**	**2014 (PMDA)**
Products Name	**Biograstim, Ratiograstim, Tevagrastim**	**Zarzio, Filgrastim Hexal**	**Nivestim**	**Filgrastim BS (Fuji), (Mochida)**	**Filgrastim BS (Teva)**	**Accofil, Grastofil**	**Filgrastim BS (Sandoz)**
Reference Products	**Neupogen**			**Gran**		**Neupogen**	**Gran**
Study Type	**2 PK/PD Studies**	**4 PK/PD Studies**	**2 PK/PD Studies**	**1PK/PD, 2PK, 1PD**	**3 PK, 2 PD studies**	**4 PK/PD Studies**	**2 PK/PD, 2PD Studies**
Primary + Secondary Objective	Equivalence in PD + PK	Equivalence in PD/PK + Safety	Equivalence in PD/PK + Safety	Equivalence in PD or PK + Safety	Equivalence in PD/PK + Safety	Equivalence in PD/PK + Safety	Equivalence in PD or PK + Safety
Study Subject	Healthy Male/ Healthy Adults	Healthy Adults	Healthy Adults	Healthy Male	Healthy Male	Healthy Adults	Healthy Male
Study Design	Randomized, single-center, single-blind, 2-period, **2-arm crossover** - Single SC 5, 10 μg/kg - Single IV 5, 10 μg/kg	Randomized, double-blind, **2-way crossover** - Single SC 1 μg/kg - Multiple SC 2.5, 5 μg/kg/d - Multiple SC 10 μg/kg/d - Single IV 5 μg/kg	Randomized, single-center, open-label, active-controlled, **2-way crossover** - Single IV & SC 10 μg/kg Randomized, single-center, double-blind, active-controlled, **2-way crossover** - Multiple SC 5 or 10 μg/kg	Randomized, open-label, active-controlled, 2-period, **2-arm crossover** (PK/PD) - Single SC 400 μg/m^2 Randomized, double-blind, active-controlled, 2-period, **2-arm crossover** (PK) - Single IV 200 μg/m^2 (PD) - Multiple SC 400 μg/m^2/d	Randomized, single-blind, 2-period, **2-arm crossover** (PK) - Single SC 300 μg/m^2 - Single SC 150 μg/m^2 - Single SC 300 μg/m^2 (PD) - Single SC 300 μg/m^2 - Multiple SC 300 μg/m^2/d	Randomized, double-blind, active controlled, **2-way cross-over** - Single SC 75, 150 μg - Single IV 5 μg/kg Randomized, double-blind, active and placebo-controlled **parallel group** - Single SC 5 μg/kg Randomized, single-center double-blind, active-controlled, **3-arm crossover** - Multiple SC 300 μg	Randomized, double blind, 2-period-**2-way crossover** (PK/PD) - Single-dose SC 5 μg/kg, - Single-dose IV 2.5 μg/kg (2PD) - Multiple doses SC 5 μg/kg/d, BID, for 3 days
Primary Endpoint	***[PK]*** AUCt of filgrastim ***[PD]*** AUCt and Cmax of ANC	***[PK]*** AUCt and Cmax of filgrastim ***[PD]*** AUC of ANC	***[PK]*** AUCt of filgrastim ***[PD]*** AUC of ANC at Day 5	***[PK]*** AUCt and Cmax of filgrastim ***[PD]*** Cmax of ANC & CD34+cell	***[PK]*** AUCt and Cmax of filgrastim ***[PD]*** Cmax of ANC & CD34+cell	***[PK]*** AUCt and Cmax of filgrastim ***[PD]*** AUCt and Cmax of ANC	***[PK]*** AUCt and Cmax of filgrastim ***[PD]*** AUECt and Emax of ANC (& CD34+ cell)
Equivalence Margin	90% CI for the test/reference GMR of the primary PK/PD endpoint needs to be within [**80-125%]** of the reference product						
NOTE		- For PD primary endpoints: 95% CIs for test/reference GMR are within *predefined equivalence intervals*, 2.5 μg/kg/d (87.3 - 114.6%) & 5 and 10 μg/kg/d (86.5 - 115.6%)		- Cmax of CD34+: **95%** CI for the T/R ratio of PD endpoint needs to be within 80-125% of the reference product		- The Phase I 3-arm study: Apo-Filgrastim(test), EU-approved Neupogen and US-licensed Neupogen	- PD endpoint: **95%** CI for the T/R ratio needs to be within 80-125% of the reference product

Abbreviation: ANC, absolute neutrophil count; AUC, area under the concentration-time curve; AUCt, area under the concentration-time curve over the dosing interval; AUEC, area under the effect curve; CI, confidence interval; Cmax, maximum serum concentration; GMR, geometric mean ratio IV, intravenous infusion; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous; T/R, test/reference

* **A Summary of FDA approved biosimilar "Zarxio" is on page 35**

Attachment 3A. Selected Summary of Regulatory Biosimilar Reviews by Year

FILGRASTIM ② Clinical Efficacy / Safety Studies*							
Approved Year (Agency)	**2008 (EMA)**	**2009 (EMA)**	**2010 (EMA)**	**2012 (PMDA)**	**2013 (PMDA)**	**2014 (EMA)**	**2014 (PMDA)**
Products Name	**Biograstim, Ratiograstim, Tevagrastim**	**Zarzio, Filgrastim Hexal**	**Nivestim**	**Filgrastim BS (Fuji), (Mochida)**	**Filgrastim BS (Teva)**	**Accofil, Grastofil**	**Filgrastim BS (Sandoz)**
Reference Products	**Neupogen**			**Gran**		**Neupogen**	**Gran**
Study Type	**1 pivotal, 2 supportive comparative studies**	**1 supportive non-comparative study**	**1 pivotal study**	**1 non-comparative study**	*The applicant did not conduct any efficacy clinical trials.* *Just submitted overseas clinical study data as reference for safety evaluation*	**1 non-comparative study**	*The applicant did not conduct any efficacy clinical trials in Japan.* *Just submitted overseas clinical study data as reference for safety evaluation*
Primary + Secondary Objective	Equivalence in efficacy + Safety + PK subgroup	Safety, tolerability and immunogenicity + Efficacy	Equivalence in efficacy + Safety, tolerability and immunogenicity	Safety + Efficacy		Safety + Efficacy	
Study Subject	Chemotherapy-naïve breast cancer patients (stage 2, 3, 4 according to AJCC classification) receiving **docetaxel & doxorubicin** CTX			Chemotherapy-naïve breast cancer patients receiving **epirubicin & 5-FU & cyclophosphamide** for pre- or postoperative CTX		Chemotherapy-naïve breast cancer receiving **docetaxel & doxorubicin & cyclophosphamide** CTX	
Study Design	Randomized, multinational, multicenter, **placebo- and active-controlled**	Randomized, multicenter open-label, single-arm	Randomized, multicenter, double-blind, **active-controlled**	***Non*-randomized**, multicenter, open-label		Randomized, multicenter open-label	
Primary Endpoint	***[Efficacy]*** DSN (ANC <0.5x10^9 /L) in days in CTX cycle 1. ***[Safety]*** Incidence of adverse events, vital signs, formation of G-CSF antibodies, lab results	***[Efficacy]*** DSN in CTX cycles 1 to 4 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-CSF antibodies, lab results	***[Efficacy]*** DSN (ANC <0.5x10^9 /L) in days in CTX cycle 1 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-CSF antibodies, lab results	***[Efficacy]*** DSN (ANC <1x10^9 /L) in days in CTX cycle 2 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-CSF antibodies, lab results		***[Efficacy]*** DSN (ANC <0.5x10^9 /L) in days in CTX cycle 1 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-CSF antibodies, lab results	
Statistics	Equivalence	Not applicable	Equivalence	Not applicable		Not applicable	
Equivalence Margin	2-sided 95% CI for least square mean difference in DSN (Test–Neupogen) lies entirely in **[-1day(-SD), +1day(+SD)]**	Not applicable	2-sided 95% CI for least square mean difference in DSN (Test–Neupogen) lies entirely in **[-1day(-SD), +1day(+SD)]**	Not applicable		Not applicable	

Attachment 3A. Selected Summary of Regulatory Biosimilar Reviews by Year

NOTE	- Full double-masking was not possible - **In pivotal study,** DSN is confirmed by assay sensitivity in comparing test drug vs placebo - **2 other supportive studies** in patients with lung cancer and NHL focused on safety	- PK/PD results are considered sufficiently comparable to support biosimilarity effect since ANC curves are superimposeable whatever the route and the dose - This trial was non comparative and therefore of limited usefulness for comparability assessment		- Patients: stage I, II or III [General Rules for Clinical and Pathological Recording of Breast Cancer September 2008 (16th ed.)] - Efficacy evaluation standard: 1-sided 97.5% CI of the DN in CTX cycle 2 not exceeds a threshold value of 3.0 days	- Safety study data of Tevagrastim® (Teva Pharmaceutical, Israel) submitted as reference for safety evaluation	- Efficacy data was not considered to provide significant support to the pivotal PD data from the phase 1 studies - This trial was non comparative and therefore of limited usefulness for comparability assessment	- Safety study data of EP06-301(clinical efficacy and safety study of Zarzio®) submitted as reference for safety evaluation

Abbreviation: AJCC, American Joint Committee on Cancer; ANC, absolute neutrophil count; CI, confidence interval; CTX, chemotherapy; DSN, duration of severe neutropenia; NHL, non-Hodgkin lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; SD, standard deviation; 5-FU, fluorouracil

* **A Summary of FDA approved biosimilar "Zarxio" is on page35**

Attachment 3A. Selected Summary of Regulatory Biosimilar Reviews by Year

FILGRASTIM		
	① Clinical Pharmacokinetic / Pharmacodynamic Studies	② Clinical Efficacy / Safety Studies
Approved Year (Agency)	**2015 (FDA)**	
Products Name	**Zarxio**	
Reference Products	**Neupogen (US and EU)**	
Study Type	**5 PK/PD studies (1 US, 4 EU)**	**1 comparative pivotal,** **2 supportive non-compartive studies** (1 in patients with CTX, 1 in patients with PBPC mobilization therapy as post-authorization safety study)
Primary + Secondary Objective	Equivalence in PK/PD + Safety, tolerability and immunogenicity	Non-inferiority in clinical effectiveness + Safety, tolerability, immunogenicity + PK sub-study
Study Subject	Healthy Adults	Chemotherapy-naïve breast cancer receiving **docetaxel & doxorubicin & cyclophosphamide** CTX
Study Design	Randomized, double-blind, 2-way crossover - Single SC 1 μg/kg (EU-source Neupogen) - Multiple SC 2.5, 5 μg/kg/d (EU-source Neupogen) - Multiple SC 10 μg/kg/d (EU-source Neupogen) - Single IV 5 μg/kg (EU-source Neupogen) - Single SC 10 μg/kg (US-source Neupogen)	Randomized, multicenter, double-blind
Primary Endpoint	*[PK]* Cmax, AUClast *[PD]* Emax, AUEClast of ANC response	*[Effectiveness]* DSN (ANC <$1x10^9$/L) in days in CTX cycle 1 *[Safety]* Incidence of adverse events, vital signs, formation of G-CSF antibodies, lab results
Statistics	Equivalence	Assess **non-inferiority** at a one-sided significance level of 2.5% in the mean duration of severe neutropenia (DSN, ANC <$0.5x10^9$/L) during Cycle 1
Equivalence Margin	PK: 90% CI for the T/R arithmetic mean ratio of PD endpoint needs to be within 80-125% of the reference product PD: 95% CI for the T/R arithmetic mean ratio of PD endpoint needs to be within 80-125% of the reference product (Pre-discussed with FDA)	Lower bound of the confidence interval is above the non-inferiority margin of -1 day
NOTE	- Additionally, 1PK sub study [EP06-302] conducted during efficacy and safety trial in breast cancer patients	1 Comparative pivotal study and 1 post-authorization safety study were for the US file. *** FDA re-analyzed clinical data results as equivalence assessment: Mean DSN on Cycle 1 with two-sided 90% CI supports equivalence conclusion**

Abbreviation: ANC, absolute neutrophil count; AUC, area under the concentration-time curve; AUCt, area under the concentration-time curve over the dosing interval; AUEC, area under the effect curve; CI, confidence interval; Cmax, maximum serum concentration; GMR, geometric mean ratio IV, intravenous infusion; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous; T/R, test/reference; ANC, absolute neutrophil count; CI, confidence interval; CTX, chemotherapy; DSN, duration of severe neutropenia; PBPC, Peripheral blood progenitor cell

Attachment 3A. Selected Summary of Regulatory Biosimilar Reviews by Year

SOMATROPIN ① **Clinical Pharmacokinetic / Pharmacodynamic Studies**				
Approved Year (Agency)	**2006 (EMA)**	**2009 (Health Canada)**	**2009 (PMDA)**	**2014 (MFDS)**
Products Name	**Omnitrope**		**Somatropin BS**	**SciTropin A**
Reference Products	**Genotropin**			
Study Type	**3 PK/PD studies**	**4 PK/PD studies**	**6 PK/PD studies**	**5 PK/PD studies**
Primary + Secondary objectives	Equivalence in PK/PD	Bioequivalence in PK/PD	Bioequivalence in PK/PD	Equivalence in PK/PD
Subjects Description	Healthy Adults			
Study Design	Randomized, double-blind, placebo-controlled, **2-way crossover study** Active-controlled, randomized, double-blind, **2-way crossover studies** - Somatropin Sandoz powder vs. Genotropin - Somatropin Sandoz powder vs. Somatropin Sandoz liquid	Active-controlled, **2-arm crossover trials** - Omnitrope powder vs. Genotropin - Omnitrope powder vs. Omnitrope solution Active-controlled, **3-arm crossover trials** - Omnitrope powder vs. Omnitrope solution (5 mg/1.5 mL) vs. Genotropin - Omnitrope powder vs. Omnitrope solution (10 mg/1.5 mL) vs. Genotropin	Randomized, double-blind, placebo-controlled, **2-way crossover study** Active-controlled, Randomized, double-blind, **2-way crossover studies** - SomatropinBS powder vs. Genotropin - SomatropinBS powder vs. liquid Active-controlled, Randomized, double-blind, **3-way crossover studies** SomatropinBS powder vs. SomatropinBS liquid vs. Genotropin - 2 Foreign studies - 1 Domestic study (single dose SC 0.07 mg/kg)	Randomized, double-blind, placebo-controlled, **2-way crossover study** Active-controlled, Randomized, double-blind, **2-way crossover studies** - Scitropin powder vs. Genotropin - Scitropin powder vs. Scitropin liquid Active-controlled, Randomized, double-blind, **3-way crossover studies** - Scitropin powder vs. Scitropin liquid (3.3 mg/mL) vs Genotropin - Scitropin powder vs. Scitropin liquid (6.7 mg/mL) vs Genotropin
	All administered at a single SC 5 mg		All administered at a single SC 5 mg except 1 domestic study	All administered at a single SC 5 mg
Primary Endpoints	***[PK]*** AUC and Cmax ***[PD]*** IGF-1, IGFBP-3, NEFA	***[PK]*** N/A ***[PD]*** IGF-1, IGFBP-3, NEFA	***[PK]*** AUC and Cmax ***[PD]*** IGF-1, IGFBP-3, NEFA	***[PK]*** AUC_{inf} and Cmax ***[PD]*** IGF-1, IGFBP-3, NEFA
Equivalence Margin	[PK] The acceptance range for the 90% CI was defined as 0.80-1.25 for AUC and Cmax. [PD] Not possible	N/A	90% CI of AUC and Cmax needs to be within 80-125%	90% CI of AUC and Cmax needs to be within 80-125%

Attachment 3A. Selected Summary of Regulatory Biosimilar Reviews by Year

NOTE	- Pharmacodynamic equivalence margin was not possible due to the following reasons. 1) endogenous GH was suppressed only part of the study duration 2) the variance of the measured parameters was high 3) pre-defined or generally accepted equivalence margin are missing	- Omnitrope powder (5.8 mg/mL)	-The margin was determined to be reasonable considering the followings. 1) Generally, 20% of difference in bioavailability shows no clinical meanings. 2) Guidelines on bioequivalence issued by Japan, the U.S., and Europe propose 0.80-1.25 as the margin of bioequivalence. 3) Somatropin is not a drug of narrow therapeutic range.	

Abbreviation: AUC, area under the concentration-time curve; CI, confidence interval; Cmax, maximum serum concentration; GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein 3; N/A, not available; NEFA, nonesterified fatty acid; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous

Attachment 3A. Selected Summary of Regulatory Biosimilar Reviews by Year

SOMATROPIN ② Clinical Efficacy / Safety Studies				
Approved Year (Agency)	**2006 (EMA)**	**2009 (Health Canada)**	**2009 (PMDA)**	**2014 (MFDS)**
Products Name	**Omnitrope**		**Somatropin BS**	**SciTropin A**
Reference Products	**Genotropin**			
Study Type	**2 pivotal efficacy comparative studies, 1 follow-up comparative efficacy study, 1 pivotal safety non-comparative study**	**3 comparative studies, 2 non-comparative studies**	**3 comparative studies, 2 non-comparative studies**	**2 pivotal studies, 1 comparative study, 2 non-comparative studies**
Primary Objective + secondary objectives	Similarity in efficacy + Long-term safety + Immunogenicity	Efficacy + Long-term safety + Immunogenicity	Efficacy + Long-term safety + Immunogenicity	Similarity in efficacy + Safety + Immunogenicity
Subjects Description	Children with growth hormone deficiency			
Study Design	Open-label, randomised, active-controlled, multicenter comparative studies - (Pivotal studies) Somatropin Sandoz powder vs. Genotropin - (Follow-up trial) Somatropin Sandoz powder → switched to Somatropin Sandoz liquid at week 15 vs. Somatropin Sandoz liquid Ongoing open, multicenter, non-comparative, non-controlled study - (Pivotal safety study) Omnitrope lyophilized formulation	Open-label, randomized, three sequential, parallel studies - Omnitrope powder continued beyond 9 months → switched to Omnitrope solution after 15 months Single-arm studies - Omnitrope solution - Omnitrope	Open-label, randomized, three sequential, multicenter studies - SomatropinBS powder vs. Genotropin - (Follow-up trial) SomatropinBS powder vs. Somatropin liquid Multicenter, non-comparative studies - SomatropinBS powder - SomatropinBS liquid	Open-label, randomized, active-controlled comparative studies - (Pivotal studies) Scitropin powder vs. Genotropin - (Supportive study) Scitropin powder vs. Scitropin liquid Multicenter, non-comparative studies - Scitropin powder - Scitropin liquid
	All administered at a dose of SC 0.03 mg/kg/day (0.1 IU/kg/day)			
Primary Endpoints	***[Efficacy]*** - Height, HSDS at month 9 - HV, HVSDS between month 0 and 9 ***[Safety]*** Adverse events, anti-human GH antibody, anti-host cells proteins antibody	***[Efficacy]*** HV, HVSDS, height standardized for age and sex standard deviation score, serum levels of IGF-1 and IGFBP-3 ***[Safety]*** Adverse events/adverse drug reactions, anti- host cell peptides antibodies	***[Efficacy]*** HV, HVSDS, HSDS, height at 0, 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 48 and 60 months ***[Safety]*** Adverse events, ISR, Anti-drug antibody, Neutralizing antibody at 0, 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 48 and 60 months	***[Efficacy]*** HV, HVSDS, GSDS, height at month 6 and 9 ***[Safety]*** Anti-drug antibody, Neutralizing antibody
Statistics	Similarity	N/A	N/A	Similarity
Equivalence Margin	N/A	N/A	N/A	N/A

Attachment 3A. Selected Summary of Regulatory Biosimilar Reviews by Year

NOTE	**- One phase 3 comparative study consisting of three sub-studies**: **Arm 1**: Somatroin Sandoz Powder → Somatropin Sandoz Powder → Somatropin Sandoz solution **Arm 2**: Genotropin → Somatropin Sandoz Powder → Somatropin Sandoz solution	- Omnitrope powder (5.8 mg/mL) - Omnitrope solution (5 mg/1.5 mL) - **Arm A in three parallel studies**: Omnitrope powder → Omnitrope powder → Omnitrope solution - **Arm B in three parallel studies**: Genotropin → Omnitrope solution → Omnitrope solution	- SomatropinBS powder (5.8 mg/mL) - SomatropinBS solution (5 mg/1.5 mL) - **Arm A in three parallel studies**: SomatropinBS powder → SomatropinBS powder → SomatropinBS solution - **Arm B in three parallel studies**: Genotropin → SomatropinBS solution → SomatropinBS solution	

Abbreviation: GH, growth hormone; GSDS, growth standard deviation score; HSDS, height standard deviation score; HV, height velocity; HVSDS, height velocity standard deviation score; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein 3; ISR, injection site reaction; IU, international unit; N/A, not available; SC, subcutaneous

Attachment 3A. Selected Summary of Regulatory Biosimilar Reviews by Year

INFLIXIMAB ① **Clinical Pharmacokinetic / Pharmacodynamic Studies**						
Approved Year (Agency)	**2012 (MFDS)**	**2013 (EMA)**	**2014 (EMA)**	**2014 (Health Canada)**	**2014 (Health Canada)**	**2014 (PMDA)**
Products Name	**Remsima**	**Remsima**	**Inflectra**	**Remsima**	**Inflectra**	**Infliximab BS**
Reference Products	**Remicade**					
Study Type	**1 PK study**	**1 pivotal, 2 supportive PK studies**		**1 pivotal PK study**		**1 Japanese, 3 abroad (1 pivotal, 2 supportive) PK studies**
Primary + Secondary objective	Equivalence in PK					
Study Subject	Patients with AS	AS patients with active disease (supportive studies: RA patients with active disease and inadequate response to MTX while receiving MTX)				Patients with active AS (Japanese and supportive abroad studies: patients with active RA while receiving MTX)
Study Design	N/A	Prospective Phase 1, randomized, double-blind, multicenter, parallel-group - Multiple single-dose IV infusion		Randomized, double-blind, multicenter, parallel-group		Randomized, double-blind, parallel-group, comparative - Multiple dose IV infusion
Primary Endpoint	***[PK]*** AUCτ, Cmax,ss between Weeks 22 and 30			***[PK]*** AUCτ, Cmax,ss		***[PK]*** Japanese study: AUCτ at Week 6-14 and Cmax at Week 6)
	[PD] N/A	***[PD]*** (Supportive study: Markers of disease activity: CRP, rheumatoid factor, ESR, anti-CCP concentration at Week 14 and 30)		***[PD]*** N/A		***[PD]*** N/A
Equivalence Margin	N/A	Equivalence; 2-sided equivalence margin of 80-125% for AUCτ and Cmax,ss in all-randomized population		N/A		(Japanese study: Equivalence; 2-sided equivalence margin of 80-125% for AUCτ and Cmax,ss)
NOTE				When the primary endpoints were assessed not mentioned in the assessment report		Primary endpoints and equivalence margin of pivotal PK study not mentioned in the assessment report

Abbreviation: anti-CCP, antibodies against cyclic citrullinated peptide; AS, ankylosing spondylitis; AUCτ, area under the concentration-time curve over the dosing interval; Cmax.ss, maximum serum concentration at steady state; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IV, intravenous; MTX, methotrexate; N/A, not available; PD, pharmacodynamics; PK, pharmacokinetics; RA, rheumatoid arthritis

Attachment 3A. Selected Summary of Regulatory Biosimilar Reviews by Year

INFLIXIMAB ② Clinical Efficacy / Safety Studies						
Approved Year (Agency)	**2012 (MFDS)**	**2013 (EMA)**	**2014 (EMA)**	**2014 (Health Canada)**	**2014 (Health Canada)**	**2014 (PMDA)**
Products Name	**Remsima**	**Remsima**	**Inflectra**	**Remsima**	**Inflectra**	**Infliximab BS**
Reference Products	**Remicade**					
Study Type	**1 comparative study**	**1 pivotal, 1 supportive comparative studies**				**1 pivotal abroad, 1 supportive Japanese comparative study**
Primary + Secondary objective	Equivalence in efficacy and safety					
Study Subjects	Patients with RA	RA patients with active disease and inadequate response to MTX while receiving MTX (supportive study: patients with active AS)				
Study Design	N/A	Prospective Phase 3, randomised, double-blind, multicentre, parallel-group - Multiple single-dose IV infusion		Randomized, double-blind, multicentre, parallel-group		Phase 3, randomised, double-blind, parallel-group, comparative
Primary Endpoint	***[Efficacy]*** % patients achieving ACR20 at week 30 ***[Safety]*** - Adverse events (infections, malignant tumor and lymphoproliferative diseases, heart failure, Infusion-related reactions, infusion-related reactions after reinfusion, delayed reactions/reaction after reinfusion, liver and biliary system, antinuclear antibodies) - Anti-infliximab antibodies	***[Efficacy]*** % patients achieving ACR20 response at week 30 (supportive study: proportion of patients achieving clinical response according to the ASAS 20 and ASAS40 criteria at Week 14 and 30) ***[Safety]*** - Adverse events, death, hypersensitivity via vital signs, electrocardiogram, physical examination, clinical laboratory tests, concomitant medications, signs and symptoms of tuberculosis, pregnancy, infections, infusion-related reactions, safety issues of special interest for infliximab - Anti-drug antibodies, neutralising anti-drug antibodies		***[Efficacy]*** Proportion of ACR20 responders at Week 30 (supportive study: proportions of patients achieving an ASAS 20 response (an improvement of ≥20%) at Week 30) ***[Safety]*** Adverse events, serious adverse event, treatment-emergent adverse events		***[Efficacy]*** % patients achieving ACR20 response at week 30 (supportive study: % patients achieving ACR20/ACR50/ACR70 response at Week 14, 30, and 54) ***[Safety]*** - Adverse events, serious adverse event, death, active tuberculosis - Anti-drug antibodies, neutralizing anti-drug antibodies at Week 14, 30, and 54
Statistics	Equivalence					
Equivalence Margin	N/A	95% CI for the difference in ACR20 contained within the equivalence margin of -15% to 15% in per-protocol population				
NOTE	Equivalence margin not mentioned in the assessment report					

Abbreviation: ACR, American College of Rheumatology; AS, ankylosing spondylitis; ASAS, assessment of spondyloarthritis International Society; IV, intravenous; MTX, methotrexate; N/A, not available; PD, pharmacodynamics; PK, pharmacokinetics; RA, rheumatoid arthritis

INSULIN GLARGINE ① **Clinical Pharmacokinetic / Pharmacodynamic Studies**		
Approved Year (Agency)	**2014 (EMA)**	**2014 (PMDA)**
Products Name	**Abrasia**	**Insulin glargine BS**
Reference Products	**Lantus**	
Study Type	**6 PK/PD studies** (3 pivotal studies, 3 supportive studies)	**6 PK/PD studies** (1 study for evaluation, 5 supportive studies)
Primary + Secondary Objective	Equivalence in PD + PK	Equivalence in PD + PK
Study Subjects	Healthy adult male and female	Foreign healthy volunteers or T1DM patients
Study Design	[Pivotal studies] Randomized, double-blind, single dose, crossover, 24-hour euglycemic glucose clamp studies in single centers - 2-treatment (LY2963016 and EU-approved Lantus) - 2-treatment (EU-approved Lantus and US-approved Lantus) - 2-treatment (LY2963016 and US-approved Lantus) [Supportive studies] Randomized, double-blind, single dose, crossover, 24-hour euglycemic glucose clamp studies in single centers - 4-treatment (at two additional dose levels) - Duration of action studies in patients	[Pivotal study] Randomized, double-blind, single dose, crossover, 24-hour euglycemic glucose clamp study - 2-treatment [Supportive studies] N/A
Primary Endpoint	***[PK]*** $AUC_{0-24h,}$ $AUC_{0-\infty,}$ Cmax ***[PD]*** Gtot, Rmax	***[PK]*** $AUC_{0-24h,}$ Cmax ***[PD]*** Gtot, Rmax
Statistics	Equivalence	
Equivalence Margin	90% CIs within the pre-specified interval 0.80 to 1.25	90% CIs within the pre-specified interval 0.80 to 1.25
NOTE		

Abbreviation: AUC, area under the concentration-time curve; CI, confidence interval; Cmax, maximum serum concentration; Gtot, total amount of glucose infused ; N/A, not available; PD, pharmacodynamics; PK, pharmacokinetics; Rmax, maximum glucose infusion rate; T1DM, type 1 diabetes mellitus

Attachment 3A. Selected Summary of Regulatory Biosimilar Reviews by Year

INSULIN GLARGINE ② Clinical Efficacy / Safety Studies		
Approved Year (Agency)	**2014 (EMA)**	**2014 (PMDA)**
Products Name	**Abrasia**	**Insulin glargine BS**
Reference Products	**Lantus**	
Study Type	**2 comparative studies**	**2 comparative studies** (1 study for evaluation, 1 supportive study)
Primary, Secondary Objective	Non-inferiority in efficacy + safety	Non-inferiority in efficacy + safety
Study Subjects	T1DM T2DM	[Evaluation study] Foreign and Japanese T1DM patients [Supportive study] Foreign T2DM patients
Study Design	Phase 3, prospective, randomized, multicenter, 2-arm, active-control, parallel studies - Open label - Double-blind	[Evaluation study] Phase 3, randomized, parallel study - Open label [Supportive study] N/A
Primary Endpoint	***[Efficacy]*** Change in HbA1c (%) at 24 weeks % of patients achieving HbA1c target <7.0% or ≤6.5%at 24 weeks ***[Safety]*** AEs, study discontinuations, hypoglycaemic episodes, injection site reactions, serious AEs, deaths, treatment-related AEs	***[Efficacy]*** Change in HbA1c (%) at 24 weeks ***[Safety]*** AEs, study discontinuations, hypoglycaemic episodes, injection site reactions, serious AEs, deaths
Statistics	Non-inferiority	
Equivalence Margin	0.05 two-sided 0.3% non-inferiority margin with 90% power (the same sample size needed to show 0.4% non-inferiority margin with > 99% power)	95% CIs for 0.4% non-inferiority margin
NOTE		

Abbreviations: AEs, adverse events; CI, confidence interval; HbA1c, glycated hemoglobin; N/A, not available; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

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Drug	Approval Agency				
	EMA	FDA	HEALTH CANADA	PMDA	MFDS
Erythropoietin	■ Abseamed (2007) ■ Binocrit (2007) ■ Epoetin alfa hexal (2007) ■ Retacrit (2007) ■ Silapo (2007)			■ Epoetin alfa BS (2010)	
Filgrastim	■ Tevasgrastim (2008) ■ Ratiograstim (2008) ■ Biograstim (2008) ■ Zarzio (2009) ■ Filgrastim hexal (2009) ■ Nivestim (2010) ■ Accofil (2014) ■ Grastofil (2014)	■ Zarxio (2015)		■ FilgrastimBS (Fuji, 2012) ■ FilgrastimBS (Teva, 2013) ■ FilgrastimBS (Sandoz, 2014)	
Somatropin	■ Omnitrope (2006)		■ Omnitrope (2009)	■ Somatropin BS (2009)	■ SciTropin A (2014)
Insulin	■ Abasaglar (2014)			■ Insulin glargine BS (2015)	
Infliximab	■ Remsima (2013) ■ Inflectra (2014)		■ Inflectra (2014) ■ Remsima (2014)	■ Infliximab BS (2014)	■ Remsima (2012)
Trastuzumab					■ Herzuma (2014)
Etanercept					■ Davigtrel (2014)

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ERYTHROPOIETIN - EMA		
Approved Year	**2007**	**2007**
Products Name	**Abseamed, Binocrit, Epoetin alfa Hexal**	**Retacrit, Silapo**
Study Type	**5 PK/PD studies** **(1 pilot study, 2 pivotal study)**	**2 PK studies**
Objectives	Equivalence in PK + PD	Equivalence in PK + Safety
Subjects	Healthy Adult Male	Healthy Adults
Study Design	Randomized, two-center, open**, parallel-group study** - Multiple IV 100 IU/kg TIW Randomized, monocentric, open, **parallel-group study** - Multiple SC 100 IU/kg TIW	**2-period cross-over study** - Single-dose IV bolus injection **3-period cross-over study** - Single-dose SC bolus injection
Primary Endpoints	***[PK]*** AUCτ of EPO	***[PK]*** $AUC_{0\text{-}tlast}$
	[PD] Absolute Hgb response (AUEC)	***[PD]*** Reticulocyte count
Equivalence Margin	**The post hoc acceptance range of 80-125%**	**The post hoc acceptance range of 80-125% for AUC & 70-143% for Cmax**
Clinical Efficacy / Safety Studies		
Study Type	**1 pivotal comparative study,** **1 supportive non-comparative study**	**2 pivotal comparative studies,** **2 supportive, uncontrolled safety studies** ****1 additional comparative SC study (2009) for Retacrit® only**
Objectives	Therapeutic equivalence in efficacy + safety	Therapeutic equivalence in efficacy + safety
Study Subjects	Renal anemia on HD	Renal anemia on HD
Study Design	Randomized, double blind, multicenter, **parallel-group** - IV study	[Correction phase IV study] Randomized, double-blind, multi-center, verum-controlled, **parallel-group study** - Multiple-dose IV [Maintenance phase IV study] Randomized, double-blind, multi-national, verum-controlled, **cross-over study** - Multiple-dose IV **[Additional maintenance phase SC study] Randomized, double-blind, multi-national, **parallel-group study** - Multiple-dose SC

Primary Endpoints	***[Efficacy]*** Mean absolute change in Hgb levels between the screening/baseline period and the evaluation period ***[Safety]*** Incidence of adverse events, serious adverse event, treatment-emergent adverse events, death, physical exam, clinical lab tests	***[Efficacy]*** [Correction phase IV study] - Mean Hgb levels during the last four -weeks of treatment - Mean weekly dosage of EPO per kg body weight during the last four weeks of treatment [Maintenance phase IV study] - Intra-individual change (test-reference) in mean weekly dosage per kg body weight of each product during the double-blind treatment period - Intra-individual change (test-reference) in mean Hgb level during double-blind treatment with each study drug **[Maintenance phase SC study] - Mean Hgb levels during the last four -weeks of treatment - Mean weekly dosage of EPO per kg body weight during the last four weeks of treatment ***[Safety]*** Occurrence of anti-epoetin antibodies, incidence of Hgb levels above 13 g/dl, ratings of tolerability, evaluation of adverse events
Statistics; Equivalence Margin	Equivalence; equivalence margin of ± 0.5 g/dl in Hgb (mean baseline Hgb = < 11.5 and > 11/5 g/dl) **Pre-defined acceptance ranges for equivalence margin*	[Correction phase IV study] Equivalence; 95% CI of the difference between both treatment groups of the primary endpoints; equivalence margin of ± 1g/dl in Hgb and ± 45 IU/kg/week (*corrected from 14 IU/kg/week) for mean weekly EPO dosage [Maintenance phase IV study] Equivalence; 2-sided 95% CI of the intra-individual change (test-reference); Equivalence margin of ± 0.6 g/dl in Hgb and ± 14 IU/kg/week for mean weekly EPO dosage [Maintenance phase SC study] Equivalence; 95% CI of the difference between both treatment groups of the primary endpoints; equivalence margin of ± 0.5 g/dl in Hgb and ± 45 IU/kg/week for EPO dosage **Pre-defined acceptance ranges for equivalence margin*

Abbreviations: AUEC, area under the effect curve; AUC, area under the concentration-time curve; CI, confidence interval; Cmax, maximum serum concentration; EPO, epoetin; HD, hemodialysis Hgb, hemoglobin; IU, international unit; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous; TIW, three times a week

Attachment 3B. Selected Summary of Regulatory Biosimilar Reviews by Agent

FILGRASTIM - ① EMA				
Approved Year	**2008**	**2009**	**2010**	**2014**
Products Name	**Biograstim, Ratiograstim, Tevagrastim**	**Zarzio, Filgrastim Hexal**	**Nivestim**	**Accofil, Grastofil**
Clinical Pharmacokinetic / Pharmacodynamic Studies				
Study Type	**2 PK/PD studies**	**4 PK/PD studies**	**2 PK/PD studies**	**4 PK/PD studies**
Objectives	Equivalence in PD + PK	Equivalence in PD/PK + Safety	Equivalence in PD/PK + Safety	Equivalence in PD/PK + Safety
Subjects	Healthy Male/ Healthy Adults	Healthy Adults	Healthy Adults	Healthy Adults
Study Design	Randomised, single-centre, single-blind, 2-period, **2-arm crossover** - Single SC 5, 10 μg/kg - Single IV 5, 10 μg/kg	Randomised, double-blind, **2-way crossover** - Single SC 1 μg/kg - Multiple SC 2.5, 5 μg/kg/day - Multiple SC 10 μg/kg/day - Single IV 5 μg/kg	Randomised, single-centre, open-label, active-controlled, **2-way crossover** - Single IV & SC 10 μg/kg Randomised, single-centre, double-blind, active-controlled, **2-way crossover** - Multiple SC 5 or 10 μg/kg	Randomised, double-blind, active controlled, **2-way cross-over** - Single SC 75, 150 μg - Single IV 5 μg/kg Randomised, double-blind, active and placebo-controlled **parallel group** - Single SC 5 μg/kg Randomized, single-center, double-blind, active-controlled, **3-arm crossover** - Multiple SC 300 μg
Primary Endpoints	***[PK]*** AUCt of filgrastim	***[PK]*** AUCt and Cmax of filgrastim	***[PK]*** AUCt of filgrastim	***[PK]*** AUCt and Cmax of filgrastim
	[PD] AUCt and Cmax of ANC	***[PD]*** AUC of ANC	***[PD]*** AUC of ANC at Day 5	***[PD]*** AUCt and Cmax of ANC
Equivalence Margin	**90% CI** for the test/reference ratio of the primary PK/PD endpoint needs to be within **80-125%** of the reference product *(Different equivalence margins are defined in PD studies of Zarzio and Filgrastim Hexal. 2.5 μg/kg/day: 87.25~114.61%, 5 and 10 μg/kg/day: 86.50~115.61%)*			
Clinical Efficacy / Safety Studies				
Study Type	**1 pivotal, 2 supportive comparative studies**	**1 supportive non-comparative study**	**1 pivotal study**	**1 non-comparative study**
Objectives	Equivalence in efficacy + Safety, PK subgroup	Safety + Efficacy	Equivalence in efficacy + Safety	Safety + Efficacy
Study Subjects	Chemotherapy-naïve breast cancer (Stage II, III, IV) patients receiving docetaxel & doxorubicin (supportive studies: in patients with lung cancer and NHL focused on safety)	Chemotherapy-naïve breast cancer patients (stage 2, 3, 4 according to AJCC classification) receiving **docetaxel & doxorubicin**		Chemotherapy-naïve breast cancer receiving docetaxel & doxorubicin & *cyclophosphamide*
Study Design	Randomised, multinational, multicentre, placebo- and active- controlled	Randomised, multicenter, open-label, single-arm	Randomised, multicentre, double-blind, active-controlled	Randomised, multicenter, open-label

Attachment 3B. Selected Summary of Regulatory Biosimilar Reviews by Agent

Primary Endpoints	***[Efficacy]*** DSN (ANC <0.5x10^9 /L) in days in cycle 1 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-SCF antibodies, lab results	***[Efficacy]*** Incidence and DSN in cycles 1 to 4 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-SCF antibodies, lab results	***[Efficacy]*** DSN (ANC <0.5x10^9 /L) in days in cycle 1 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-SCF antibodies, lab results	
Statistics; Equivalence Margin	Equivalence; 2-sided 95% CI for least square mean difference in DSN (Test–Neupogen) lies entirely in **[-1day(-SD), +1day(+SD)]**	N/A	Equivalence; 2-sided 95% CI for least square mean difference in DSN (Test–Neupogen) lies entirely in **[-1day(-SD), +1day(+SD)]**	N/A

Abbreviation: AJCC, American Joint Committee on Cancer; ANC, absolute neutrophil count; AUC, area under the concentration-time curve; CI, confidence interval; Cmax, maximum serum concentration; DSN, duration of severe neutropenia; IV, intravenous; N/A, not applicable; NHL, non-Hodgkin lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous; SD, standard deviation

FILGRASTIM - ② PMDA			
Approved Year	**2012 (PMDA)**	**2013 (PMDA)**	**2014 (PMDA)**
Products Name	**Filgrastim BS (Fuji), Filgrastim BS (Mochida)**	**Filgrastim BS (Teva)**	**Filgrastim BS (Sandoz)**
Study Type	**1 PK/PD, 2 PK, 1 PD studies**	**3 PK, 2 PD studies**	**2 PK/PD, 2PD studies**
Objectives	Equivalence in PD or PK + Safety	Equivalence in PD or PK + Safety	Equivalence in PD or PK + Safety
Subjects	Healthy Male		
Study Design	Randomised, open-label, active-ontrolled, 2-period, **2-arm rossover** (PK/PD) Single SC 400 μg/m^2 Randomised, double-blind, active-controlled, 2-period, **2-arm crossover** (2PK) single IV 200 μg/m^2 (PD) multiple SC 400 μg/m^2/day	Randomised, single-blind, 2-period, **2-arm crossover** (3PK) - Single SC 300 μg/m^2 , 150 μg/m^2 , 300 μg/m^2 (2PD) - Single SC 300 μg/m^2 - Multiple SC 300 μg/m^2/day	Randomized, double blind, 2-period-**2-way crossover** (2PK/PD) Single-dose SC 5 μg/kg, IV 2.5 μg/kg (2PD) Multiple doses SC 5 μg/kg/day, BID, for 3days
Primary Endpoints	***[PK]*** AUCt and Cmax of filgrastim	***[PK]*** AUCt and Cmax of filgrastim	***[PK]*** AUCt and Cmax of filgrastim
	[PD] Cmax of ANC & CD34+cell	***[PD]*** Cmax of ANC & CD34+cell	***[PD]*** AUECt and Emax of ANC(& CD34+ cell)
Equivalence Margin	**90% CI** for the test/reference ratio of the primary PK/PD endpoint needs to be within **80-125%** of the reference product (Cmax of CD34+: **95%** CI for the test/reference ratio of PD endpoint needs to be within 80-125% of the reference product)		**90% CI** for the test/reference ratio of the primary PK endpoint needs to be within **80-125%** of the reference product (PD endpoint: **95%** CI for the test/reference ratio needs to be within 80-125% of the reference product)
Clinical Efficacy / Safety Studies			
Study Type	**1 non-comparative study**	*The applicant did not conduct any efficacy clinical trials. Just submitted overseas clinical study data as reference for safety evaluation. Safety study data of Tevagrastim® (Teva Pharmaceutical, Israel) submitted as reference for safety evaluation*	*The applicant did not conduct any efficacy clinical trials. Just submitted overseas clinical study data as reference for safety evaluation. Safety study data of EP06-301(clinical efficacy and safety study of Zarzio®) submitted as reference for safety evaluation*
Objectives	Safety + Efficacy of test drug		
Study Subjects	Chemotherapy-naïve breast cancer patients receiving epirubicin & 5-FU & cyclophosphamide for pre- or postoperative chemotherapy		
Study Design	Non-randomised, multicenter, open-label study		
Primary Endpoints	***[Efficacy]*** DN (ANC <1x10^9 /L) in days in chemotherapy cycle 2 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-SCF antibodies, lab results		
Statistics; Equivalence Margin	N/A		

Abbreviation: ANC, absolute neutrophil count; AUEC, area under the effect curve; BID, twice a day; CI, confidence interval; Cmax, maximum serum concentration; DN, duration of severe neutropenia; IV, intravenous; N/A, not applicable; NHL, non-Hodgkin lymphoma; PD, pharmacodynamics, PK, pharmacokinetics; SC, subcutaneous; 5-FU, fluorouracil

INFLIXIMAB - ① EMA[4]		
Approved Year	**2013**	**2014**
Products Name	**Remsima (Celltrion)**	**Inflectra (Hospira)**
Reference Product	**Remicade (Janssen)**	
Clinical Pharmacokinetic / Pharmacodynamic Studies		
Study Type	**1 pivotal study** (+ Supportive PK data were generated from the pivotal efficacy trial)	
Objectives	Equivalence in PK	
Subjects	AS patients with active disease	
Study Design	Prospective Phase 1, randomised, double-blind, multicentre, multiple single-dose IV infusion, parallel-group	
Primary Endpoints	***[PK]*** AUCτ, Cmax,ss between Weeks 22 and 30	
	[PD] (supportive study: markers of disease activity: CRP, rheumatoid factor, ESR, anti-CCP concentration at Week 14 and 30)	
Equivalence Margin	Equivalence; 2-sided equivalence margin of 80% to 125% for AUCτ and Cmax,ss in all-randomised population	
Clinical Efficacy / Safety Studies		
Study Type	**1 pivotal study (+** Supportive efficacy data were collected in the pivotal PK trial conducted in AS patients)	
Objectives	Equivalence in efficacy and safety	
Study Subjects	RA patients with active disease and inadequate response to MTX while receiving MTX	
Study Design	Prospective Phase 3, randomised, double-blind, multicentre, multiple single-dose IV infusion, parallel-group	
Primary Endpoints	***[Efficacy]*** % patients achieving ACR20 response at week 30 (supportive study: proportion of patients achieving clinical response according to the ASAS20 and ASAS40 criteria at Week 14 and 30) ***[Safety]*** - Adverse events, death, hypersensitivity via vital signs, electrocardiogram, physical examination, clinical laboratory tests, concomitant medications, signs and symptoms of tuberculosis, pregnancy, infections, infusion-related reactions, safety issues of special interest for infliximab - Anti-drug antibodies, neutralising anti-drug antibodies	
Statistics; Equivalence Margin	Equivalence; 95% CI for the difference in ACR20 contained within the equivalence margin of 15% in per-protocol population	

Abbreviation: ACR, American College of Rheumatology; anti-CCP, antibodies against cyclic citrullinated peptide; AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; AUCτ, area under the concentration-time curve over the dosing interval; CI, confidence interval; Cmax,ss, maximum serum concentration at steady state; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IV, intravenous; MTX, methotrexate; PD, pharmacodynamics; PK, pharmacokinetics; RA, rheumatoid arthritis

[4] Additionally, 1 pilot study (CT-P13 1.2) was also conducted. This study (randomised, double-blind, parallel-group, Phase 1) was designed to provide preliminary data on the initial pharmacokinetics, efficacy, and safety of CT-P13 compared with Remicade when co-administered with methotrexate in patients with active rheumatoid arthritis.

INFLIXIMAB - ② Health Canada		
Approved Year	**2014**	**2014**
Products Name	**Remsima (Celltrion)**	**Inflectra (Hospira)**
Reference Product	**Remicade (Janssen)**	
Clinical Pharmacokinetic / Pharmacodynamic Studies		
Study Type	**1 pivotal PK study**	
Objectives	Equivalence in PK	
Subjects	Patients with active AS	
Study Design	Randomised, double-blind, multicentre, parallel-group	
Primary Endpoints	***[PK]*** AUCτ, Cmax,ss	
	[PD] N/A	
Equivalence Margin	N/A	
Clinical Efficacy / Safety Studies		
Study Type	**1 pivotal study (+** Supportive efficacy data were collected in the pivotal PK trial conducted in AS patients)	
Objectives	Equivalence in efficacy and safety	
Study Subjects	RA patients with active disease and inadequate response to MTX while receiving MTX	
Study Design	Randomized, double-blind, multicentre, parallel-group	
Primary Endpoints	***[Efficacy]*** Proportion of ACR20 responders at Week 30 (supportive study: proportions of patients achieving an ASAS20 response (an improvement of ≥20%) at Week 30) ***[Safety]*** Adverse events, serious adverse event, treatment-emergent adverse events	
Statistics; Equivalence Margin	Equivalence; minimal treatment differences with 95% CIs falling within the ACR20 (Week 30) comparability margins of -15% to 15% in per-protocol population	

Abbreviation: ACR, American College of Rheumatology; AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; AUCτ, area under the concentration-time curve over the dosing interval; CI, confidence interval; Cmax,ss, maximum serum concentration at steady state; MTX, methotrexate; N/A, not applicable; PD, pharmacodynamics; PK, pharmacokinetics