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

July 25, 2016

Table of Contents

1. Position Statement

The Biosimilar Working Group of the International Pharmaceutical Regulators Forum (IPRF BWG) prepared this Reflection Paper (hereby the Paper). The IPRF BWG suggests that the National Regulatory Agencies (NRAs) that participate in the IPRF consider the proposed principles in the Paper on the extrapolation of indication(s) in the authorization of biosimilar products (also known as follow-on biologics, subsequent entry biologics or similar biological medicinal products, etc.).

The Paper addresses the issues associated with the extrapolation of indications, proposes principles for the extrapolation and considerations of the proposed principles in the approval of biosimilar products. The Paper also includes the proposed scope of regulatory submissions for a biosimilar product applicant to receive the approval of an extrapolated indication(s). However, this Paper does not deal with the definition of the terminology associated with biosimilar products, the regulatory requirements in demonstrating biosimilarity, or other issues on the authorization of biosimilar products, which are subject to the policies and procedures on the biosimilar product regulations by each NRA.

The other hand, although decision-making is driven by scientific considerations, legal or public health frameworks and clinical practice vary in different countries. For example, indication that are still under patent or data protection in Canada would not be granted a Notice of Compliance until such protections expire.

2. Executive Summary

A stepwise approach is normally recommended throughout a biosimilar development programme, 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 clinical data is to address slight differences shown at previous steps and to confirm comparable clinical performance of the biosimilar and the reference (medicinal) product.

The reference product may have more than one therapeutic indication. When biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable. The clinical study population should be representative of the approved therapeutic indication(s) of the reference product and be sensitive for detecting potential differences between the biosimilar and the reference product.

The IPRF BWG considers that the extrapolation of indication(s) of a biosimilar product could be accepted on the basis of the totality of the evidence generated from analytical, non-clinical and clinical comparability data.

It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by thorough physicochemical, structural and biological analysis as well as appropriate clinical data in one therapeutic indication and that the mechanism of action is the same or sufficiently similar across the extrapolated indication(s). 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 scientific and regulatory principle that has been exercised for many years, e.g. in the case of major changes in the manufacturing process of originator products. In the context of biosimilars, the majority of NRAs are in agreement with accepting the extrapolation of indication(s) 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 of indication(s) based on that evidence. Furthermore, the conclusions on the extrapolation of indication(s) can be differ 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 extrapolation of indication(s), despite the fact that the final regulatory decisions on the specific biosimilar applications have not always been consistent (Attachment 2). Those guidelines are essentially the same in that the extrapolation of clinical efficacy and safety data to other indications of the reference product, not specifically studied during the clinical development of the biosimilar product, would be acceptable on the basis of the comprehensive evidence of similarity data with adequate justification using the totality-of-evidence approach.

In order to improve efficiency of regulatory evaluation of biosilmilars and 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.

Most biosimilar guidelines address in common that the basis for the extrapolation of indication(s) 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 and should be largely similar between the indications. 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 the extrapolation of indication(s) for biosimilar products, which would form the scientific basis of biosimilar product development and enable access to biosimilar 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, therefore, residual uncertainties remain to be resolved, 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 assurance there are no clinically meaningful differences between them.

4.2. Principles for Extrapolation of Indications

The major objective of the extrapolation of indication(s) for a biosimilar product 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 the other benefits by reducing the quantity of clinical trial(s) that needed for the approval of the biosimilar product. Hence, the principles of extrapolation of indication(s) 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 in one indication, then extrapolation to other indication(s) of the reference product could be acceptable with an appropriate scientific justification. Without conducting confirmatory trial(s) to support each indication held by the reference product, it would be possible for an applicant to justify that their biosimilar product will likely produce essentially the same clinical outcomes 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 the extrapolation of indications:

- Whether the tested therapeutic indication is the most sensitive for detecting 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 about the considerations for 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 and additional data is necessary
- 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 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. The 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 confirmatory study or studies with 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) in one therapeutic indication, a case can be made to extrapolate safety and efficacy findings from the reference product to the biosimilar product. Additional data can 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 for differences in all relevant aspects of efficacy and safety

5.1. Evidence from Analytical Comparability Study

The extrapolation of indications 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 quality attributes in this regard may imply that there are some minor differences between the biosimilar and its reference product. Such difference(s) may trigger uncertainty for the extrapolation of indication(s). Therefore, the applicant should submit compelling evidence that any minor differences in quality attributes do not produce different safety and efficacy outcomes in different indications between the two products.

Depending on the quality data generated, an adequate justification could be required to provide assurance on the absence of (potential) residual uncertainties for the extrapolation of indication(s), particularly when the comparability study was performed using overly sensitive analytical or functional assays. Such uncertainties may imply the existence of minor differences (e.g., in post-translational modification) that could have an impact on the safety and efficacy profiles. In general, any minor differences should be identified in the early 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 in terms of the extrapolation.

An example of a minor difference in quality attibutes 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, supplemented with additional *in vitro* data. With an adequate explanation and justification, EMA accepted this difference had no impact on its efficacy and safety, which could be extended to the overall consideration of extrapolation.

The following summaries will explain the scientific basis of 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 the extrapolation of indications 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 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 clinically meaningful.

Animal studies should be avoided and would only be valuable where there is a clearly relevant species available to detect relevant differences and support the extrapolation of indication(s). 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

The extrapolation of indications can be justified on the basis that the biosimilar product has been demonstrated to be similar to its reference product in clinical studies in one or more therapeutic indication(s), and the reference product is deemed to be highly similar in therapeutic effects not only for both the indication studied but also the other indication(s) of interest.

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

- Clinical data showing highly similar profile between the proposed biosimilar and its reference product in the most sensitive clinical setting.
- 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 efficacy trial 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 the most sensitive model of disease and measurement of the most sensitive endpoint.
- Clinical data showing a comparable safety profile between the proposed biosimilar and its reference product in the most sensitive clinical setting.

  The extrapolation of safety profiles across indications may need justification because patient populations for different indications may have 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.
- Pharmacokinetic and pharmacodynamic data that show a high degree of similarity
- Extrapolation of 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).

- 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. In order to extrapolate the clinical data of one indication to other indication(s), the sensitivity of the studied indication should be adequately assessed in order to justify that this indication is the most sensitive clinical model to detect 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 submit adequate evidence to justify that such indication is the most sensitive clinical model to allow for the extrapolation of indication(s).

The clinical data obtained from a well-controlled comparative study or studies would be very pertinent to confirm the comparability established by 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 the extrapolation of indication(s) 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.
  - Efficacy and safety trial

    The patients with renal anemia without major complications (e.g., severe and chronic infections or bleeding or aluminum toxicity) are expected to distinguish the variations reasonably well between the treatment outcomes using different erythropoietin products. 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.

- Efficacy and safety trial

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.

- Efficacy and safety trial

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.

- Efficacy and safety trial

Patients with rheumatoid arthritis were considered a sensitive population to detect 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 biosimilarity 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. In this case, it would not be necessary to use the same primary efficacy endpoints as those that were used in the marketing authorization application of the reference product. Instead, it is advisable to include some common endpoints (e.g., secondary endpoints) to facilitate comparisons to the clinical trials conducted with the reference product. If such changes to endpoints are applied, the applicant should justify that the changes in endpoints are scientifically valid.

5.4. Evidence from Publicly Available Information

Publicly available information should be used to support the scientific principles associated with the extrapolation of indication(s). 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. 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

In case that it is still unclear whether the safety and efficacy aspects confirmed in one indication will likely be relevant to the other indication(s) of interest even after considering all aspects stated above, additional clinical data need to be submitted. It is expected the applicant for the biosimilar product will discuss these requirements with the NRA.

6. References

World Health Organization. *Guidelines on Evaluation of Similar Biotherapeutic Products*. Available from: http://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf?ua=1 [accessed June 7, 2016]

Brazilian Health Surveillance Agency. To be added soon from http://portal.anvisa.gov.br/wps/portal/anvisa/home

European Medicines Agency. *Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues.* Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf [accessed June 25, 2015]

Federal Service for Control over Healthcare and Social Development. To be added soon from http://www.roszdravnadzor.ru/

Health Canada. *Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics.* Available from: http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/seb-pbu/notice-avis_seb-pbu_2010-eng.php [accessed June 25, 2015]

Health Sciences Authority. *Guidance on Registration of Similar Biological Products in Singapore.* Available from: http://www.hsa.gov.sg/content/dam/HSA/HPRG/Western_Medicine/Overview_Framework_Policies/Guidelines_on_Drug_Registration/Appendix%2017_Guidance%20on%20Registration%20of%20Similar%20Biological%20Products%20in%20Singapore%202011.pdf [accessed June 25, 2015]

Ministry of Food and Drug Safety. *Guidelines on the Evaluation of Biosimilar Products, Revision 1.* Available from:

http://www.mfds.go.kr/jsp/common/download.jsp?fileinfo=S*1*동등생물의약품평가가이드

라인(개정_2014).pdf*616a492bb0544a74ecadf6a230f02df5*pdf*/files/upload/1/TB_O_ANNOUNCE/8687/616a492bb0544a74ecadf6a230f02df5*573383*2014:12:30 09:34:37 [accessed June 25, 2015]

Pharmaceuticals and Medical Devices Agency. *Guideline for the Quality, Safety, and Efficacy Assurance of Follow-on Biologics.* Available from: http://www.pmda.go.jp/files/000153851.pdf [accessed June 25, 2015]

Swissmedic. *Authorisation of Similar Biological Medicinal Products*. Available from: https://www.swissmedic.ch/zulassungen/00153/00189/00197/01810/index.html?lang=en&do

wnload=NHzLpZeg7t,lnp6I0NTU042l2Z6ln1ad1IZn4Z2qZpnO2Yuq2Z6gpJCDdoB6f2ym162epYbg2c_JjKbNoKSn6A-- [accessed June 25, 2015]

U.S. Food and Drug Administration. *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.* Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf [accessed June 25, 2015]

Recommendations, 16th International Conference of Drug Regulatory Authorities, Brazil, 26-29 August 2014 (http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/16_ICDRA_Recommendations2014.pdf?ua=1&ua=1, accessed 7 June 2016).

Weise M, Bielsky MC, De Smet K, Ehmann F, Ekman N, Giezen TJ, et al. Biosimilars: what clinicians should know. *Blood* 2012; 120(26): 5111-7

Weise M, Kurki P, Wolff-Holz E, Bielsky MC, Schneider CK. Biosimilars: the Science of Extrapolation. *Blood* 2014; 124(22): 3191-6

Concept paper on extrapolation of efficacy and safety in medicine development (EMA/129698/2012, draft)

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM431119.pdf Zarxio™ (filgrastim), Presentation to the Oncologic Drugs Advisory Committee (January 7, 2015). Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/On%20456%20cologicDrugsAdvisoryCommittee/UCM431119.pdf

Attachments

1. Gap Analyses for Biosimilar Guidelines on the Extrapolation of Indications
2. Biosimilar Products Approved with Extrapolated Indications

3A. Selected Summary of Regulatory Biosimilar Reviews by Year

- Erythropoetin, Filgrastim, Somatropin, Infliximab, Insulin

3B. Selected Summary of Regulatory Biosimilar Reviews by Agent

- Erythropoetin, Filgrastim, Infliximab

[Annex 1] Example of the totality-of-evidence approach

- 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 of indication from the renal to the cancer indication has been supported by the totality of the evidence from a comparability exercise. 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 diseases 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, PMDA and FDA granted the extrapolation of all Remicade indications[i] for the approval of biosimilar infliximab (Remsima, Celltrion), Health Canada excluded inflammatory bowel diseases in the extrapolation. This decision appears to be associated with a different interpretation of results from antibody-dependent cell-mediated cytotoxicity (ADCC) assays.

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 the extrapolation of indication(s).

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