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

[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, and following conditions should be fulfilled: - Convincing arguments if efficacy trial in non-inferiority study
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).

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	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) ■ 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.	■ 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**

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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

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○ **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)