Biosimilars
Hot Topic:
Extrapolation To Support Indications for Biosimilars

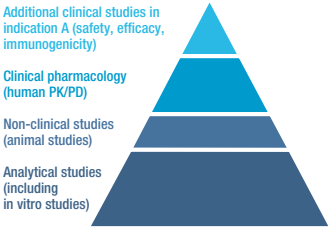
What is Extrapolation in the Context of Biosimilars?

- Extrapolation is the approval of a biosimilar for use in an indication held by the reference (originator) product not directly studied in a comparative clinical trial with the biosimilar[1,2]

Requirements for extrapolation[1,2]

Totality of evidence to demonstrate biosimilarity*

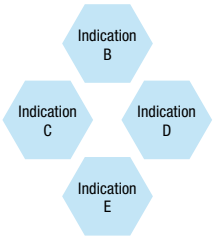
Data to demonstrate analytical similarity and no clinically meaningful differences vs reference product



Knowledge of the reference product

Prior regulatory agency finding of safety and efficacy for the reference product

Approval of additional reference product indications



Scientific justification†

Differences in the below do not preclude extrapolation, but do need to be addressed as part of the justification

1. Is the mechanism of action expected to differ across indications?
2. Do the PK and PD vary across patient populations?
3. Is the immunogenicity expected to vary in different patient populations?
4. Are there differences in expected toxicities in different indications and patient populations?

PD, pharmacodynamics; PK, pharmacokinetics.
*Clinical studies, as part of a biosimilar development program, should be performed in populations and use endpoints that are adequately sensitive to detect any clinically meaningful differences between the proposed biosimilar and the reference product

†Also considered are any other factors that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought

- While extrapolation is not automatic, it may be accepted provided the totality of evidence coupled with scientific justification and knowledge of the reference product can address any identified differences[1,2]

1 Is the mechanism of action expected to differ across indications?

Example of data considered for extrapolation

Functional similarity is demonstrated in all mechanisms of action

Mechanism of action	Indication A	Indication B	Indication C	Indication D
Soluble ligand binding and neutralization	✓	✓	✓	✓
Membrane-bound ligand binding	NA	NA	✓	✓
Effector functions (eg, ADCC or CDC)	NA	NA	✓	✓

ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; NA, not applicable
Data are for illustrative purposes only and do not represent actual data for a biologic medicinal product

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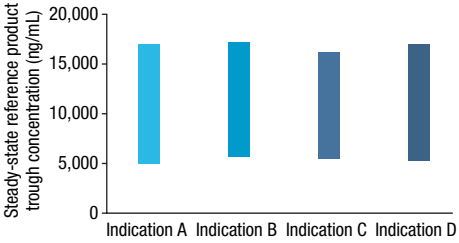
2 Do the PK and PD vary across patient populations?

Example analysis of data

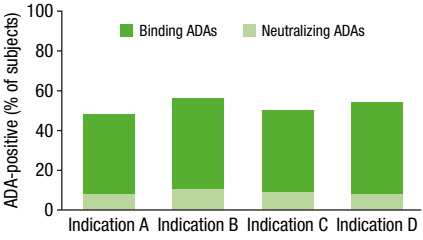
Steady-state trough concentration of the reference product is similar across indications



3 Is the immunogenicity expected to vary in different patient populations?

Example analysis of data

Immunogenicity of the reference product is generally similar across indications*



ADA, anti-drug antibody. *When compared using the same immunoassay and considering the use of immunosuppressants
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4 Are there differences in expected toxicities in different indications and patient populations?

Example analysis of data

Toxicities of the reference product are similar across indications

Data from comparative clinical trial (indication A)								
AE (Grade ≥3)	Incidence with biosimilar	Incidence with RP		Incidence reported in literature for RP in indication A	Incidence reported in literature for RP in indication B	Incidence reported in literature for RP in indication C	Incidence reported in literature for RP in indication D	Similar incidence across indications?
AE 1	2.0%	1.7%	➡	1.8%	1.6%	2.1%	2.2%	✓
AE 2	6.7%	7.1%	➡	6.8%	7.3%	6.5%	7.1%	✓
AE 3	13.0%	11.0%	➡	12.6%	14.9%	13.1%	12.0%	✓

AE, adverse event; RP, reference product
Data are for illustrative purposes only and do not represent actual data for a biologic medicinal product

Extrapolation is an essential regulatory concept for biosimilars that reduces or eliminates the requirement to study a proposed biosimilar with clinical trials in every indication of the reference product[3]

References

1. FDA. Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for industry, 2015. Available at: https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf; 2. EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf; 3. Tesser JRP, et al. *Biologics*. 2017;11:5–11. All links accessed May 2021.

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