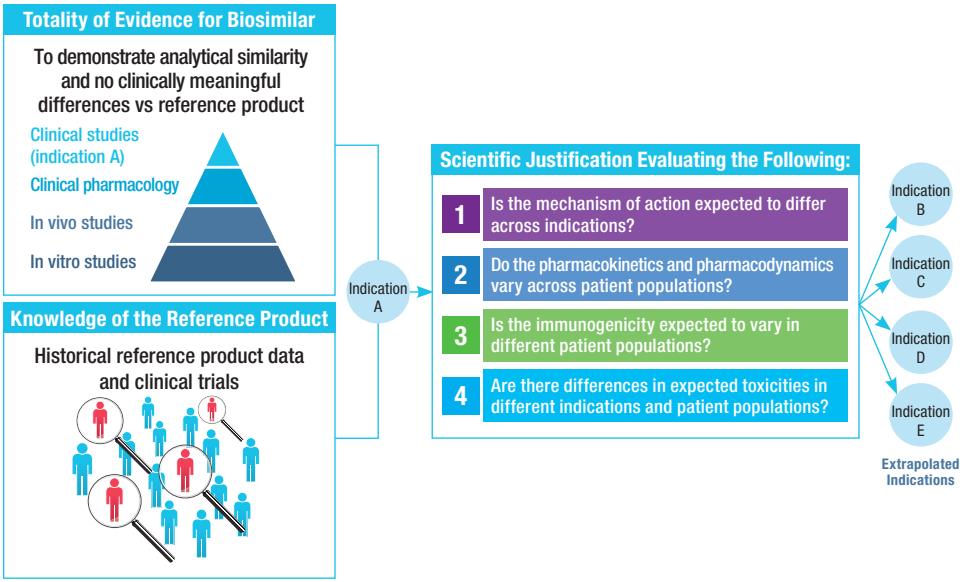
Biosimilars
Hot Topic:
Extrapolation of Indications

What is Extrapolation of Indications?

- Indication extrapolation means that a proposed biosimilar product may be licensed in one or more additional conditions for which the reference product is licensed, but for which the biosimilar itself has not been studied in clinical trials[1,2]

Regulatory Guidance Describes the Requirements for Extrapolation[1,2]



- 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

MOA	Indication 1	Indication 2	Indication 3	Indication 4
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
Data are for illustrative purposes only and do not represent actual data for a biologic medicinal product

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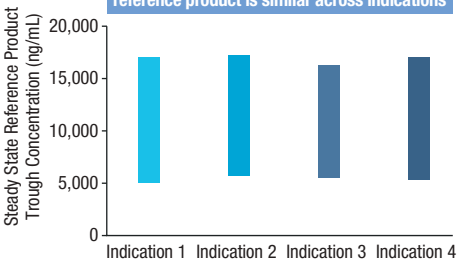
2 Do the pharmacokinetics and pharmacodynamics vary across patient populations?

Example analysis of data

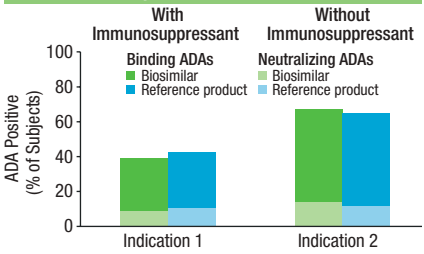
Steady state trough concentration of the reference product is similar across indications



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

Example analysis of data

Immunogenicity remains consistent between a biosimilar and its reference product in different conditions of use



ADA, anti-drug antibody; RP, reference product

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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 Phase 3 Clinical Confirmation Trial (Indication 1)								
AE (Grade ≥3)	Incidence with biosimilar	Incidence with RP		Incidence Reported in Literature for RP in Indication 1	Incidence Reported in Literature for RP in Indication 2	Incidence Reported in Literature for RP in Indication 3	Incidence Reported in Literature for RP in Indication 4	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%	11%	➡	12.6%	14.9%	13.1%	12.0%	✓

AE, adverse event

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Indication extrapolation is an essential biosimilar regulatory concept 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: Targets and Therapy 2017:11 5–11. All links accessed March 2018.

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