



Biosimilars

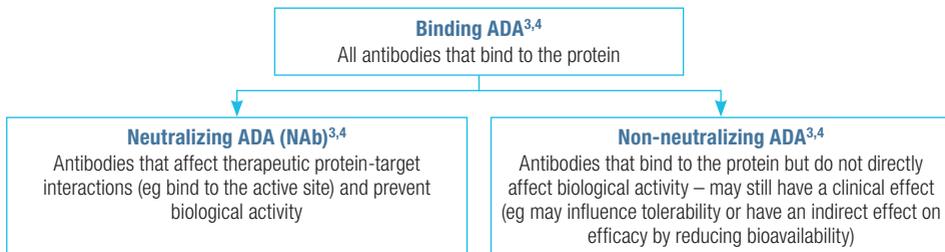
Hot Topic:

Determining Immunogenic Potential

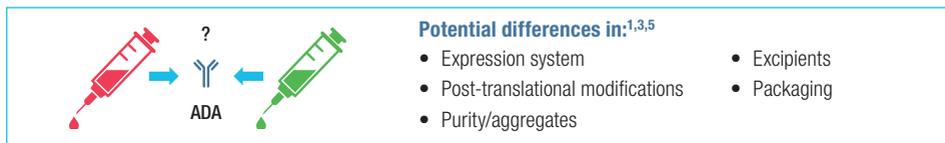


Why is the Assessment of Immunogenicity Important for Biosimilars?

- Immunogenic responses, generally manifesting as anti-drug antibodies (ADAs), can develop in patients who are treated with biologic agents, including biosimilars.¹ ADAs may influence efficacy and/or safety¹⁻³



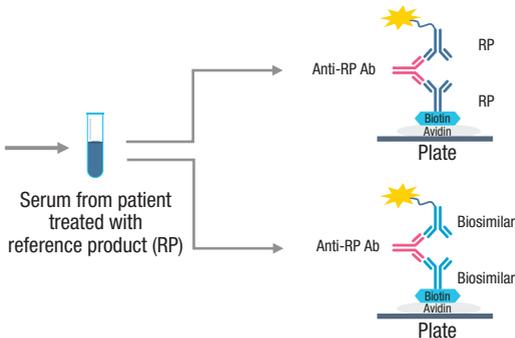
Small Differences Between a Biosimilar and the Reference Biologic Product Could Lead to Differences in the Development of ADAs^{2,3,5}



A High Degree of Similarity Between a Biosimilar and Reference Product Suggests Possible Cross-Reactivity of ADAs

- Cross-reactivity may occur from reference biologic ADA to biosimilar or from biosimilar ADA to reference biologic⁶
- ADAs may bind to the same epitope on the reference biologic and biosimilar⁶

ADA testing



Assessment of comparative immunogenicity is an essential part of the biosimilar development process^{2,5}

How is Immunogenicity of Biosimilars Assessed in Clinical Trials?

- At least one comparative, parallel-arm clinical study to assess potential differences in immunogenicity between the reference product and biosimilar is recommended^{2,3,5}

Key Considerations for Clinical Immunogenicity Testing of Biosimilars in Inflammatory Diseases^{2,4,5,7}

Patient population



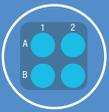
- Sufficiently sensitive to detect differences should they exist
 - Treatment-naïve patients recommended
 - Patients not receiving immunosuppressants preferred (those on immunosuppressants are less likely to develop immune responses)
 - Capable of predicting response in extrapolated indications

Duration of follow-up



- Consider time course of immune response
 - May take >6 months for neutralizing ADAs to be detected
 - 1 year follow-up generally recommended for chronically administered agents

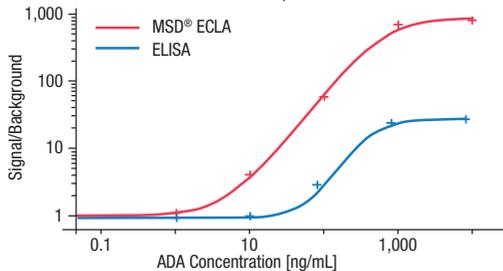
Assays to detect ADAs



- Validated
- Sufficiently sensitive
- Should assess binding and neutralizing antibodies

Assays to Detect ADAs Have Evolved Over Time to Become More Sensitive and Specific^{3,8,9}

Comparison of ECLA & ELISA Immunogenicity Assays⁹



Assay modality	ELISA	MSD ECLA
Sensitivity	Lower ~100 ng/mL	Higher ~10 ng/ml
Free drug tolerance	Lower	Higher

ECLA, Electrochemiluminescence assay; ELISA, Enzyme-linked immunosorbent assay; MSD, Meso Scale Discovery[®]
Figure reproduced with permission from Meso Scale Discovery

- ADAs have generally been detected in a larger proportion of patients when using more sensitive assays³

Immunogenicity testing aims to demonstrate that the risk of ADA development with a biosimilar is no greater than with the reference product^{2,3,5}

References

- Ben Horin S, et al. *Exp Rev Gastroenterol Hepatol* 2015;9(S1):S27-S34; 2. 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>; 3. Pineda C, et al. *BioDrugs* 2016;30:195-206; 4. FDA. Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products Guidance for Industry. Draft guidance, 2016. Available at: <https://www.fda.gov/downloads/Drugs/Guidances/UCM192750.pdf>; 5. EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf; 6. Reinisch W et al. *BioDrugs* 2017;31:223-237; 7. Fells-Giemza A & Moots R. *Rheumatology* 2015;54(11):1941-3; 8. Collet-Brose J, et al. *J Immun Res*. [published ahead of print May 3, 2016]. 2016:5069678. doi: 10.1155/2016/5069678; 9. MSD. Immunogenicity assays from Meso Scale Discovery. Available from: <https://www.mesoscale.com/~media/files/brochures/immunogenicity%20assays.pdf>. All links accessed March 2018.

