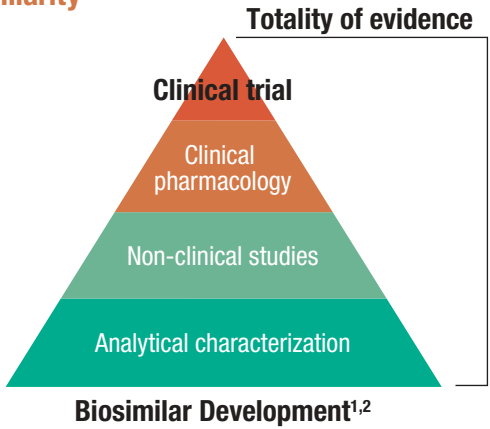
Biosimilars

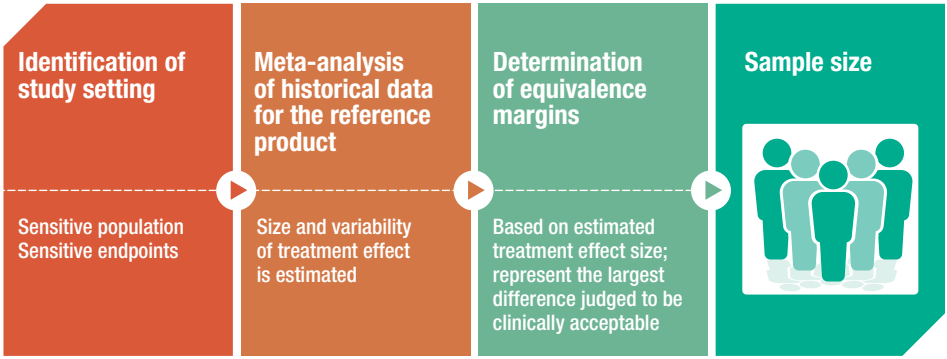
Hot Topic: Statistical Considerations for Biosimilar Equivalence Trials

A Comparative Clinical Efficacy and Safety Assessment is the Final Stage of Demonstrating Biosimilarity

- Biosimilars are approved based on the totality of evidence[1,2]
- The clinical trial aims to confirm that there are **no clinically meaningful differences** between a biosimilar and its reference product in a sensitive patient population using a sensitive endpoint[1,2]
- The trial will also assess safety outcomes[1,2]
- **Equivalence trials are recommended** to confirm biosimilarity[1,2]



During Equivalence Trial Design, a Step-by-step Approach is Used to Determine Equivalence Margins and Sample Size[3,4]



Equivalence margins are determined independently for each proposed biosimilar, following discussion and agreement between regulators and the biosimilar developer.[2]

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There are Two Common Statistical Measures Used to Assess Biosimilarity[3]

Risk difference (RD)

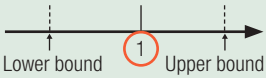
% of patients reaching endpoint with biosimilar – % reaching endpoint with reference product

- If drugs have the same efficacy, RD=0

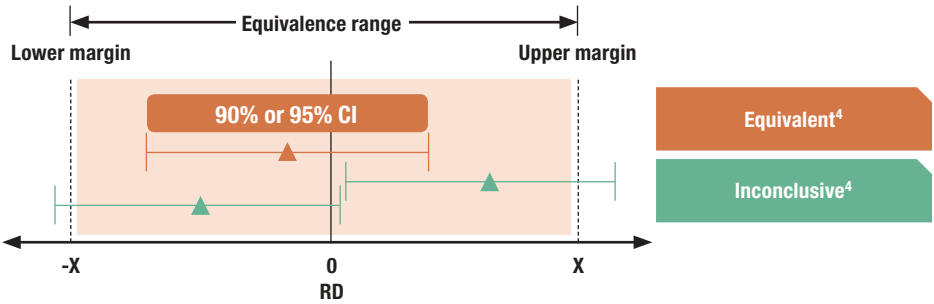
Risk ratio (RR)

$$\frac{\text{\% of patients reaching endpoint with biosimilar}}{\text{\% reaching endpoint with reference product}}$$

- If drugs have the same efficacy, RR=1



The Outcomes of RD and RR Analyses are Determined by the Predefined Equivalence Margins[1,2,5]



CI, confidence interval

Comparative clinical efficacy is shown by demonstrating that the two-sided CI for RR or RD falls within the predefined equivalence margins.[3,4,6]

References

1. 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; 2. FDA. Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for industry, 2015. Available at: http://www.fda.gov; 3. Isakov L, et al. Am J Ther 2016;23:1903–10; 4. Alten R, et al. Semin Arthritis Rheum 2015;44:S2–8; 5. ICH. Topic E 9 statistical principles for clinical trials, 1998. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf 6. He J, et al. Clin Cancer Res 2016;22:5167–70. Links accessed February 2019

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