Sandoz
Biopharmaceuticals

The way forward in biosimilar development

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Biosimilars improve access for patients

Anti-TNF	Volume increase per treatment day - 2016 vs. year before biosimilar entrance
Bulgaria	190 %
Slovakia	93 %
Sweden	74 %
Portugal	63 %
Czech	59 %

G-CSF	Volume increase per treatment day - 2016 vs. year before biosimilar entrance
Romania	2542 %
Bulgaria	581 %
Slovakia	509 %
Slovenia	178 %
Norway	164 %

EPO	Volume increase per treatment day - 2016 vs. year before biosimilar entrance
Poland	237 %
Greece	196 %
Italy	39 %
Czech	36 %
Bulgaria	36 %

HGH	Volume increase per treatment day - 2016 vs. year before biosimilar entrance
Romania	152 %
Poland	82 %
UK	79 %
Finland	70 %
Czech	68 %

Reference: QuintilesIMS. The impact of biosimilar competition on price, volume and market share Update 2017. Available at: http://bit.ly/2rpB1rW, accessed 3.9.2018

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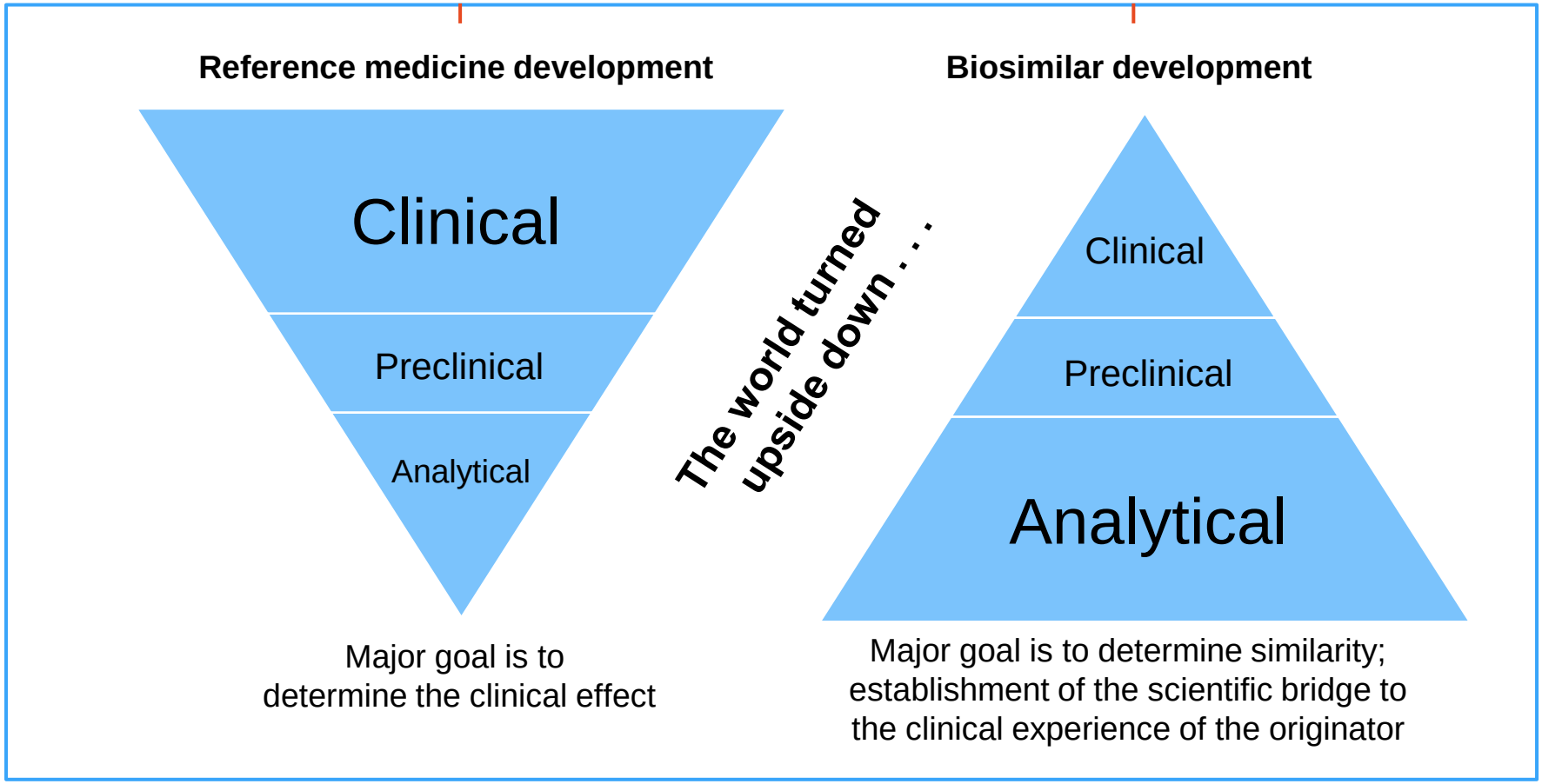
Development of a biosimilar requires a paradigm shift



Analytical methods provide the most sensitive tools to establish this scientific bridge

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Figure by Sandoz and inspired by Judith Macdonald, APEC conference, Seoul Sept 2013

Difference between developing reference and biosimilar medicine

Biological medicine with new active substance (e.g. reference medicine)	Biosimilar medicine
No previous knowledge of safety and efficacy	Builds on knowledge of safety and efficacy from years of clinical use with reference medicine
Development aims at demonstrating safety and efficacy directly in patients	Development aims at demonstrating comparable safety and efficacy by establishing biosimilarity
Comparability studies only for manufacturing changes during development (e.g. producing larger batches for clinical trials)	Comprehensive comparability studies with the reference medicine
Full non-clinical data (pharmacology and toxicology)	Amount of non-clinical data determined by the outcome of quality studies
Conventional clinical trials to demonstrate efficacy and safety in all claimed therapeutic indications	Comparative clinical trials to exclude clinically meaningful differences
Trials designed mainly to compare with placebo or current standard of therapy using 'hard' endpoints (e.g. long-term outcome, mortality, structural damage) and a relevant patient population to demonstrate benefit	Trials designed mainly to show clinical equivalence with the reference medicine using sensitive endpoints in a population where product-related differences in clinical performance can be detected
Positive benefit-risk mainly established on the basis of safety and efficacy studies in the intended population	Positive benefit-risk based on demonstrating biosimilarity (using comparability studies)

Biosimilars in the EU, Information guide for healthcare professionals; EMA and EU Commission, 2017; http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500226648 accessed 31.5.2017

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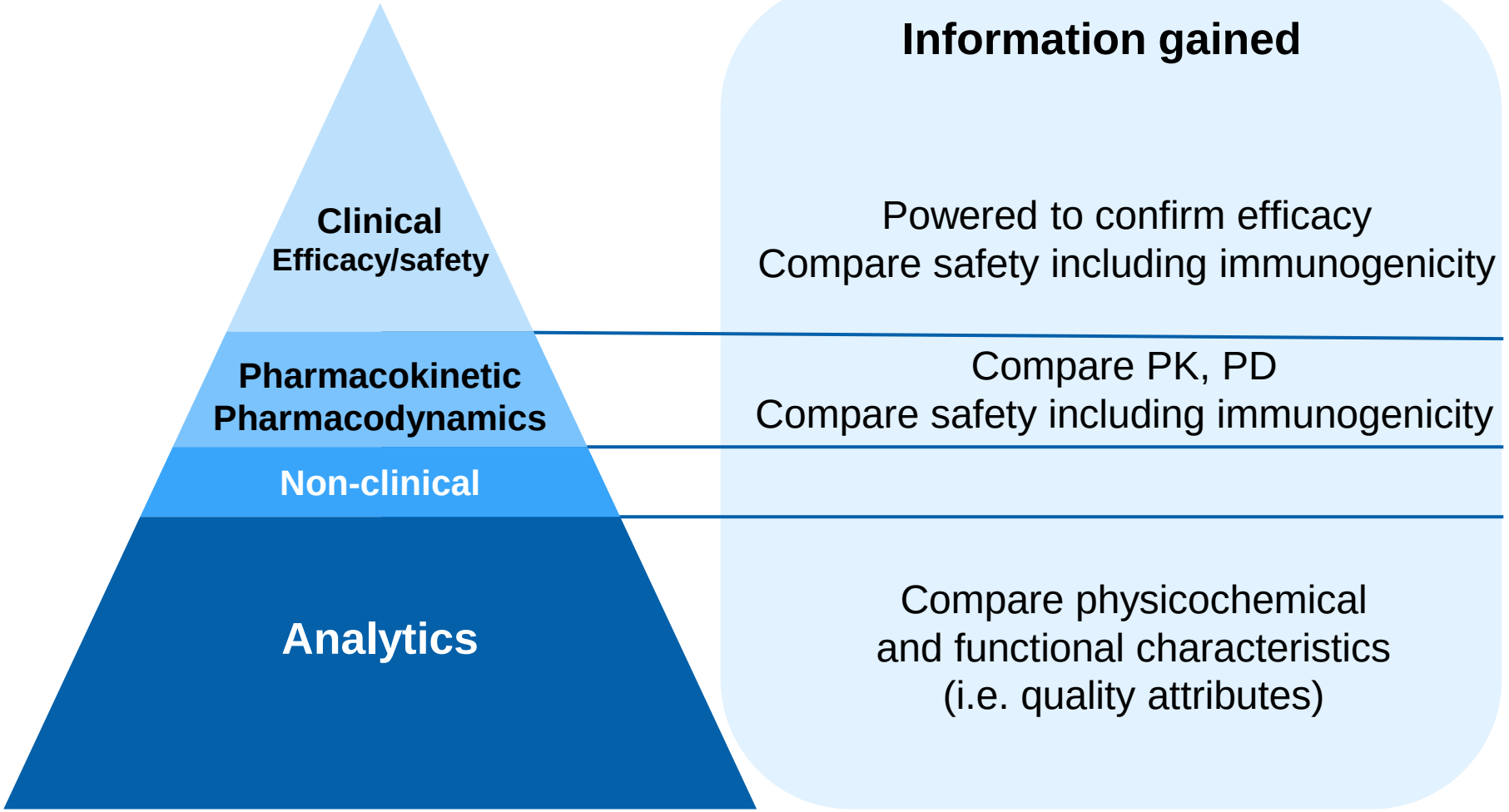
Totality of evidence



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Guidelines are open to waive Phase III type clinical studies

- "A clinical efficacy trial may not always be necessary, e.g. where there is a clinically relevant PD endpoint." [1]
- EMA provides conditions to waive phase III type trials in product specific guidelines for insulin, filgrastims, LMWH [2]
- "In certain cases, establishing a similar clinical PK, PD, and immunogenicity profile may provide sufficient clinical data to support a conclusion that there are no clinically meaningful differences between the two products." [3]

1. Health Canada biosimilar guidance 2016, https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/seb-pbu/seb-pbu-2016-eng.pdf, accessed 29.8.18
2. EMA biosimilar guidelines for rG-CSFs (rev1 draft), 2018 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/08/WC500254104.pdf; Insulins 2015 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500184161.pdf; LMWH 2016 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/11/WC500217126.pdf; accessed 29.8.18
3. FDA Biosimilar guidance 2015, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf, accessed 29.8.18

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Guidelines are open to waive Phase III type clinical studies

- Important development in regulatory sciences
  - Increase efficiency in biosimilar development
  - What is needed should be done – not less / not more
  - Enable biosimilar competition to reference products with smaller markets
- Maintain rigorous scientific standards in regulatory decision making
- Current limiting requirement
  - Availability of “relevant“ pharmacodynamic measure

1. Health Canada biosimilar guidance 2016, https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/seb-pbu/seb-pbu-2016-eng.pdf, accessed 29.8.18
2. EMA biosimilar guidelines for rG-CSFs (rev1 draft), 2018 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/08/WC500254104.pdf; Insulins 2015 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500184161.pdf; LMWH 2016 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/11/WC500217126.pdf; accessed 29.8.18
3. FDA Biosimilar guidance 2015, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf, accessed 29.8.18

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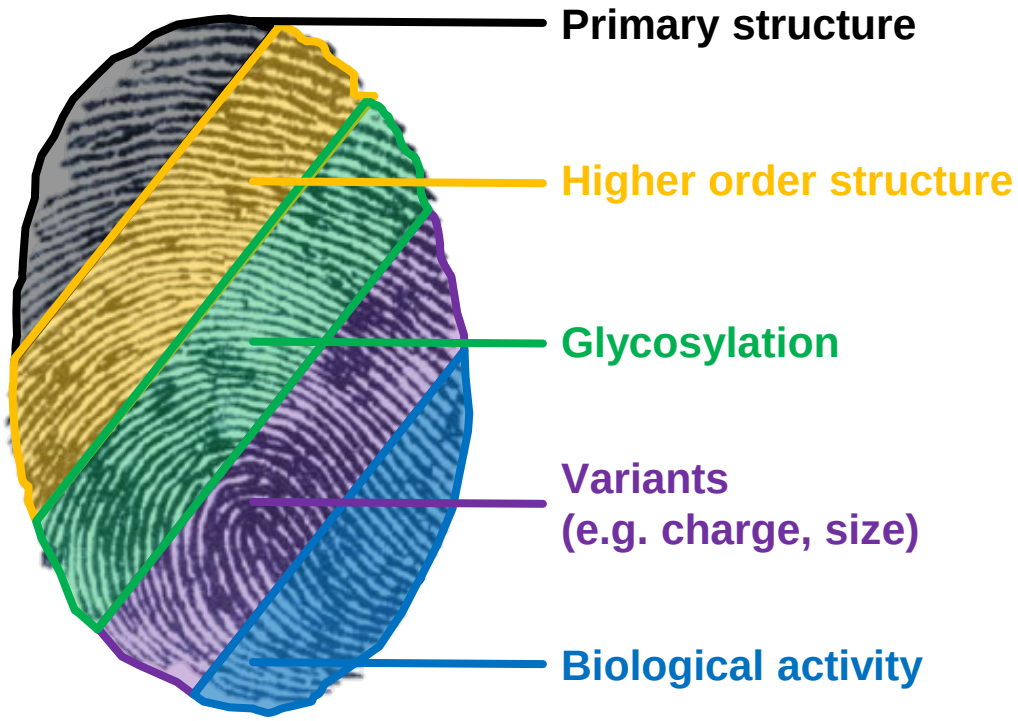
Foundation by robust analytical comparison

- Identification of all quality attributes that matter
  - Mitigate the risk of the unknown
- Suitable analytical toolbox
  - State-of-the-art methods
  - Functional in-vitro assays enabling the evaluation of the impact of physicochemical attributes on the protein function
- Comparison of analytical data, while considering the lot-to-lot variability of the reference product

The biosimilar must match the reference medicine in all relevant structural and functional attributes



Example mAb:

- More than 40 different methodologies applied
- Analyzing more than 100 different quality attributes
- Attributes are ideally measured by more than one method (redundancy)

- Windisch J. EGA's perspective on the draft quality guideline, 2013 [online] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500154191.pdf [Accessed 2016 March 18] Sandoz-generated/owned slide (November 18 2014).

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Which quality attributes matter clinically?

Criticality assessment mitigates risk of missing relevant attributes

Quality attributes related to

- **Molecule**
- **Process materials**
- **Excipients**

Assessment on clinical relevance

- **Immunogenicity**
- **Safety/Toxicity**
- **Pharmacokinetics**
- **Efficacy**

Existing product knowledge

- **Literature**
- **In-house studies**
- **Related molecules**

Criticality	Criticality score
Very high	121 - 140
High	86 - 120
Moderate	56 - 85
Low	31 - 55
Very low	2 - 30

Figures and tool by Sandoz
Concept of Critical Quality attributes: ICH Q8 guideline,
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf
accessed 28.8.18

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How to ensure comparable immunogenicity at the quality level?

- Comparable efficacy and safety of a biosimilar with its reference medicine is a basic requirement for biosimilarity This includes immunogenicity [1, 2]
- Relevant question for all biologics, e.g. when evaluating process manufacturing changes [3]
  - Learnings can be applied to biosimilar regulation

References:

1. WHO Guidelines on evaluation of similar biotherapeutic products (SBPs), 2009
2. EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, 18 Dec 2014, EMEA/CHMP/BMWP/42832/2005 Rev1
3. ICH Q5 guideline, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf, accessed 29.8.18

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Quality related risk factors for immunogenicity are well understood

Potentially clinically relevant quality attributes (examples)

- Amino acid sequence – identical for biosimilar
- Aggregates
- Folding impurities, disulphide bridges
- Degradation products
- Host cell proteins
- Leachables / extractables
- Glycosylation (non-human glycans, NGNA)
- Galactose-α1,3-Galactose
- PEG

Can be controlled at the analytical level

References:
Brocchini S, et al. Adv Drug Deliv Rev 2008;60(1):3–12; Chung CH, et al. N Engl J Med 2008;358:1109–17; Dashivets T, et al. PLoS One 2015;10:e0143520; Goetze AM, et al. MAbs 2010;2(5):500–7; Kennedy DM, et al. Clin Exp Immunol 1994;98:245–51; Liu H, May K. Mabs 2012;4:17–23; Markovic I. Expert Opin Drug Saf 2007;6:487–91; Rathore N, Rajan RS. Biotechnol Prog 2008;24(3):504–14; Ripple DC, Dimitrova MN. J Pharm Sci 2012;101:3568–79; Wang X, et al. Biotechnol Bioeng 2009;103:446–58; Weber CA, et al. Adv Drug Deliv Rev 2009;61:965–76; Wright A, et al. EMBO J 1991;10:2717–23

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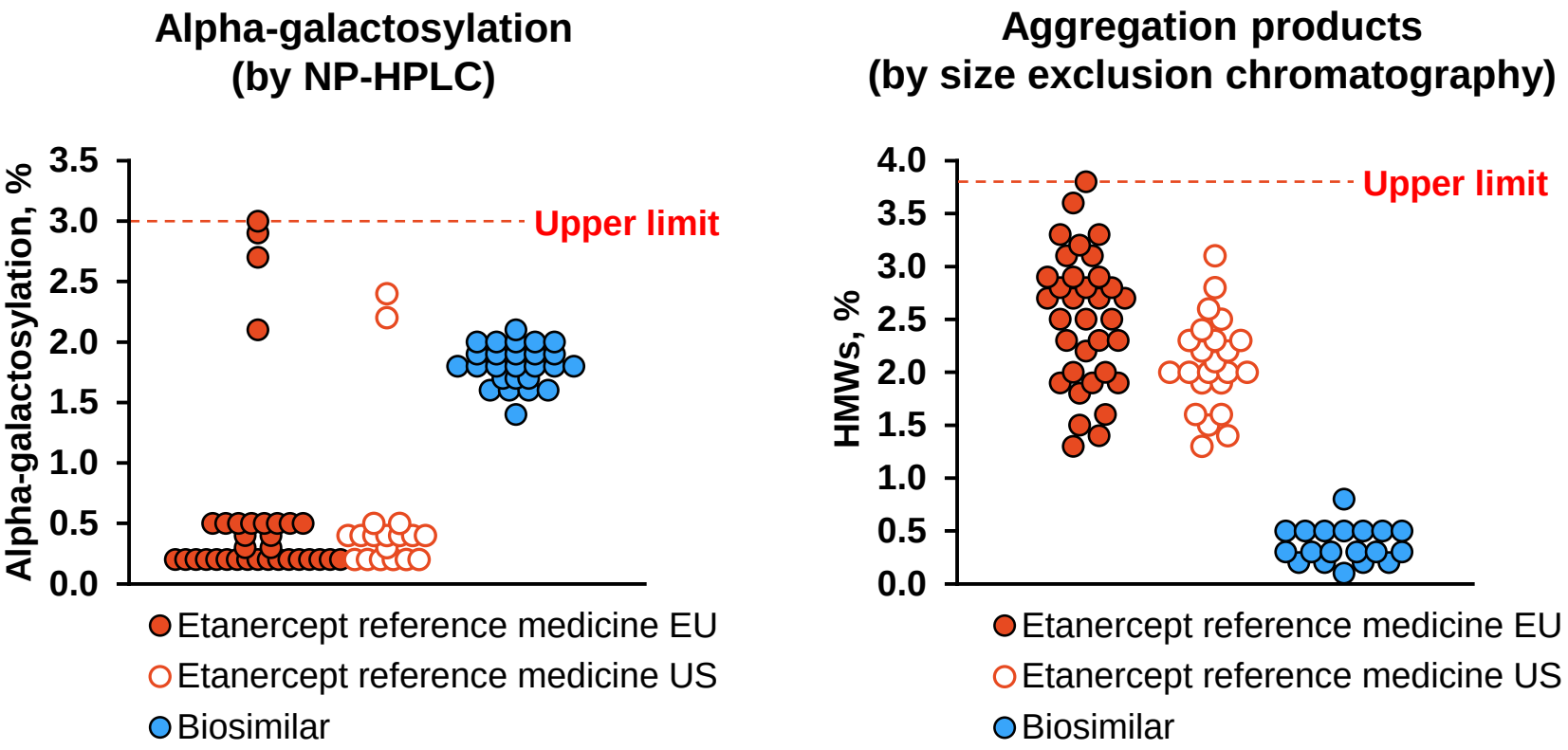
High similarity results in similar immunogenicity

Example Infliximab

- 250 patients with Rheumatoid Arthritis treated with reference medicine
- 126 developed anti drug antibodies (ADA)
- Those ADAs were cross-reactive against biosimilar infliximab CT-P13

References:
Ruiz-Argüello B, et al. Antibodies to infliximab in Remicade-treated rheumatic patients show identical reactivity towards biosimilar CT-P13. Ann Rheum Dis. 2016;75:1693-1696

Example for controlling impurities considered as potential risk factors for immunogenicity



NP-HPLC: Normal phase high performance liquid chromatography; HMW: High molecular weight variants

Adapted from slides from FDA Arthritis Advisory Committee, July 13, 2016, http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM513088.pdf, accessed 29.8.18

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How can statistical approaches support the comparison of quality attributes?

- Applicable e.g. for bioactivities, related substances, impurities
- Descriptive visual statistics
  - Plot the data and compare visually
- Comparison of ranges
  - Compare against measured, estimated or established acceptable ranges or limits
- Comparison of means
  - Equivalence test for comparable mean

Variability of major glycan variant in commercial mAb

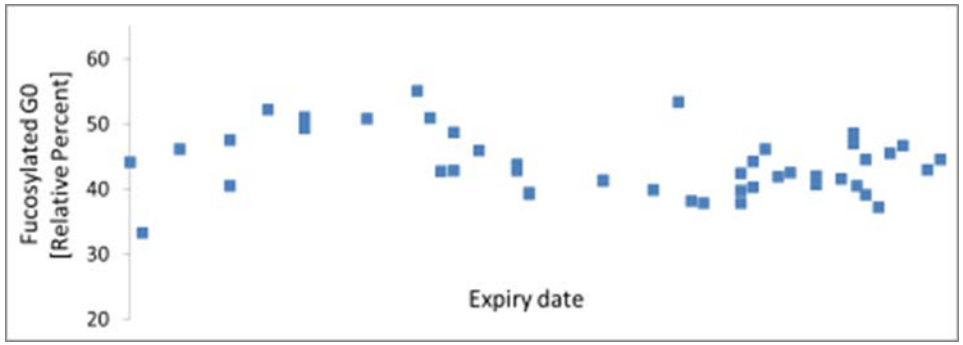

Figure developed by Thomas Stangler, Sandoz data

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Guideline developments on statistical approaches

- EMA issued draft reflection paper in March 2017 [1]
  - High level draft reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development
  - Scope includes manufacturing changes, biosimilar medicines, generics – avoids political bias
- FDA withdrew draft guidance in June 2018 [2]
  - Reflects issues with some of the concepts
    FDA announced revised draft which will include:
    - Consideration of appropriate methods to analyze analytical data to account for potential lot-to-lot variability of the reference medicine
    - Focus on providing appropriate flexibility for sponsors in order to help spur the efficient development of biosimilars without compromising the agency's rigorous scientific standards

1. EMA draft reflection paper 2017, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/03/WC500224995.pdf, accessed April 2018
2. FDA guideline withdrawal notice June 2018, https://www.fda.gov/Drugs/DrugSafety/ucm611398.htm, accessed 29.8.18

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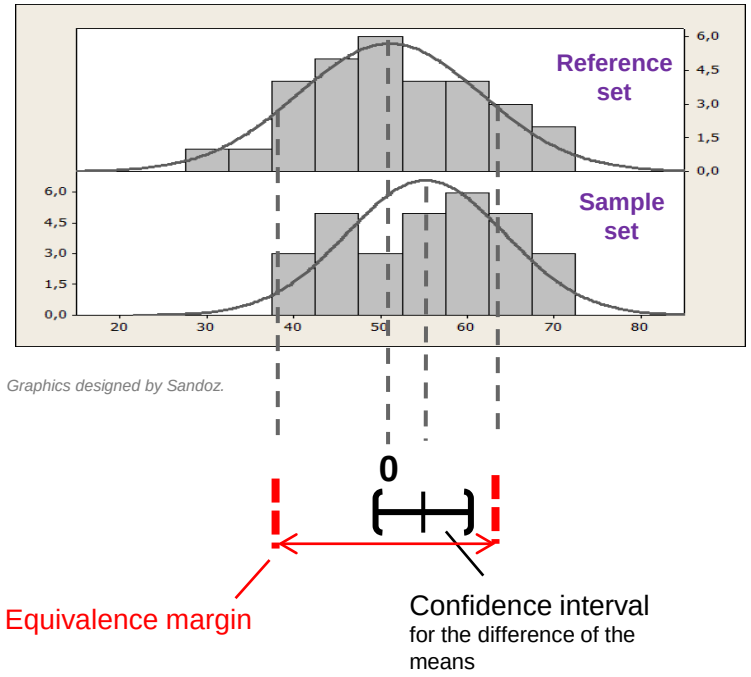
Contentious approach: Statistical test for equivalence of means

- Well established statistical approach for clinical studies
- New concept for regulating quality attributes
- Key prerequisites are often not met for quality attributes
  - Independent data
  - Identically distributed
  - Stable mean



Graphics designed by Sandoz.

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Equivalence of means
What do current guidelines tell us?

- "A critical quality attribute should be within an appropriate limit, range, or within-lot-distribution"
- The mean of different batches is not specified as a regulatory expectation
- Consequently, the mean may change over time as long as the critical quality attributes of individual batches remain within appropriate limits
  - Inherent process variability within acceptable ranges
  - Process manufacturing changes
  - Movements within an approved design space

References:
ICH Q6B guideline on specifications for biologicals, 1999
ICH Q7 guideline on GMP, 2000
ICH Q5E guideline on comparability after manufacturing changes, 2004
ICH Q8(R2) guideline on product development, 2009

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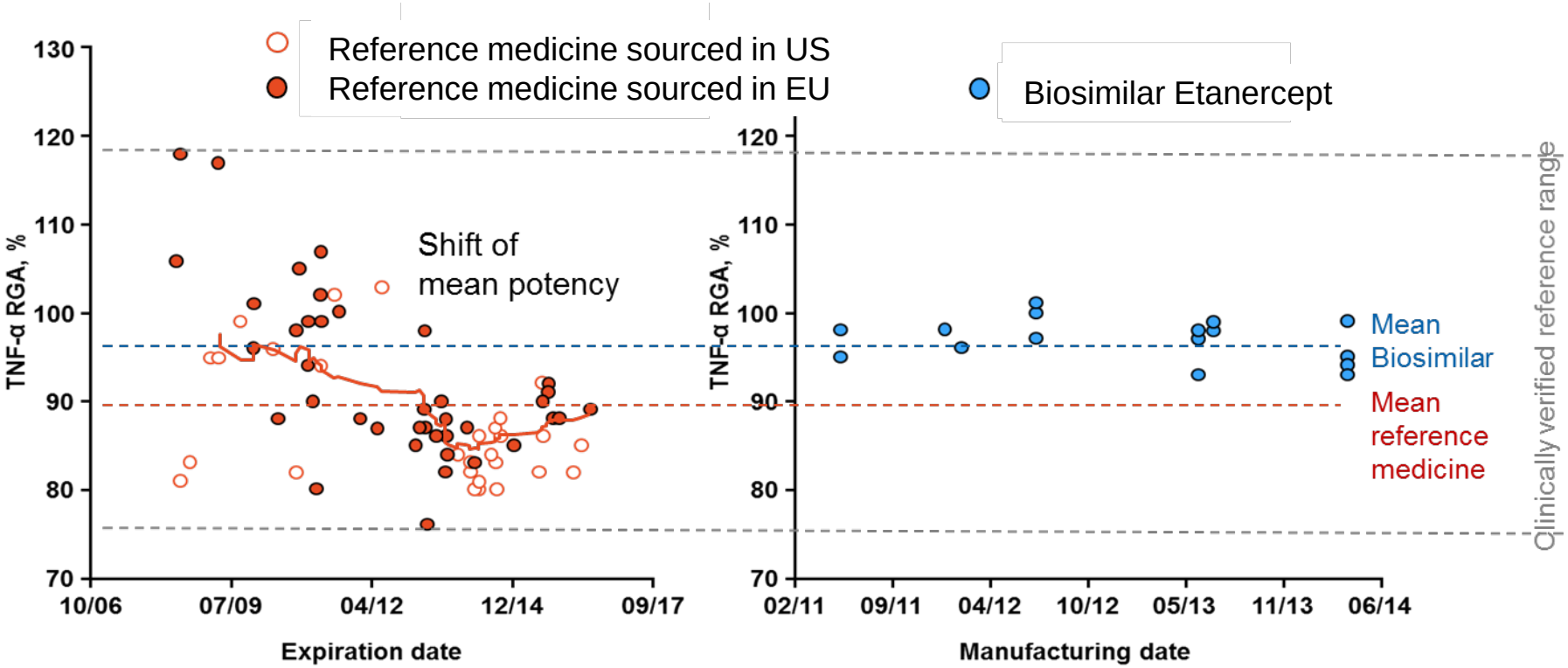
The mean can change over time - Example 1

Etanercept reference product



The red line indicates the moving average calculated by 11 to 21 data points

Example demonstrates that a strict regulatory requirement for equivalent means poses the risk to falsely reject true biosimilars

Reference: derived from Lamanna et al., Scientific Reports, 7: 3951, 2017

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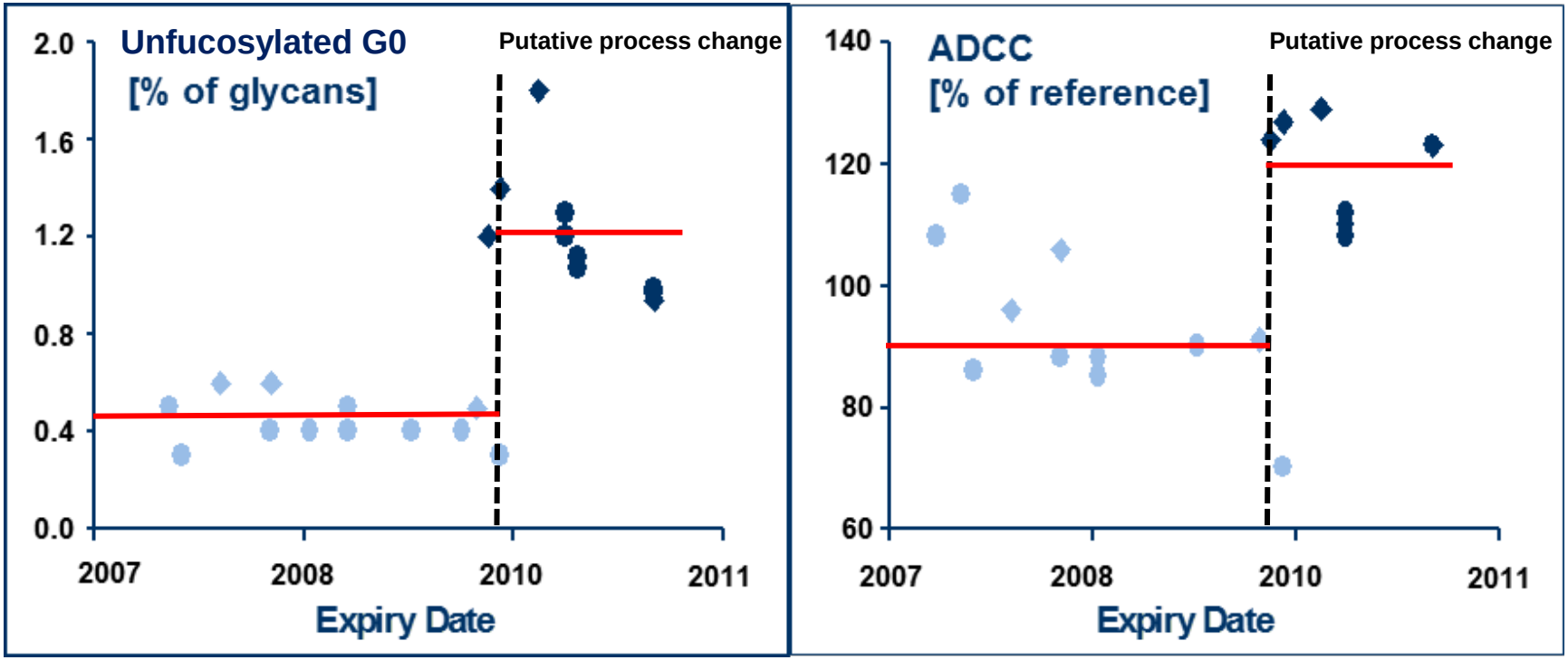
The mean can change over time Example 2

Rituximab reference medicine



The mean can change over time and still represent acceptable consistent quality

Statistics cannot serve to set pass/fail criteria for manufacturing changes

Reference: derived from Schiestl et al. Nat Biotechnol, 2011;29:310-312

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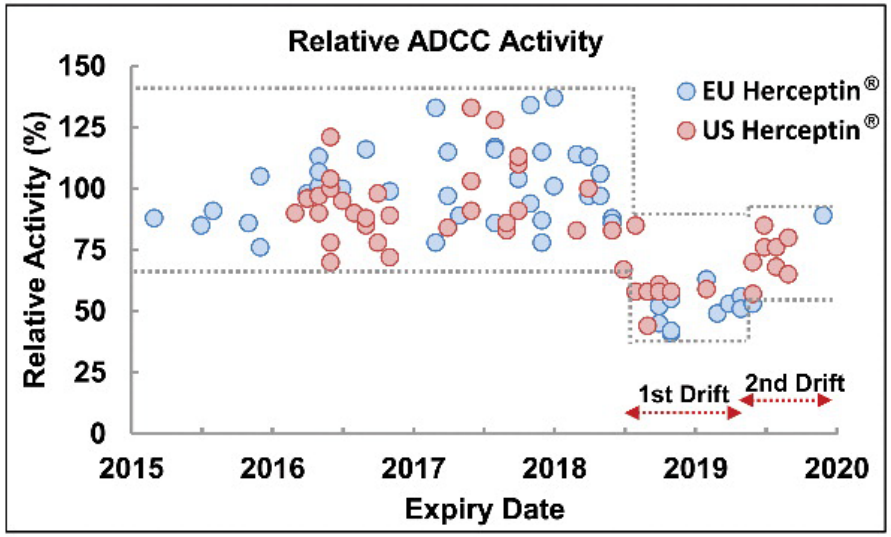
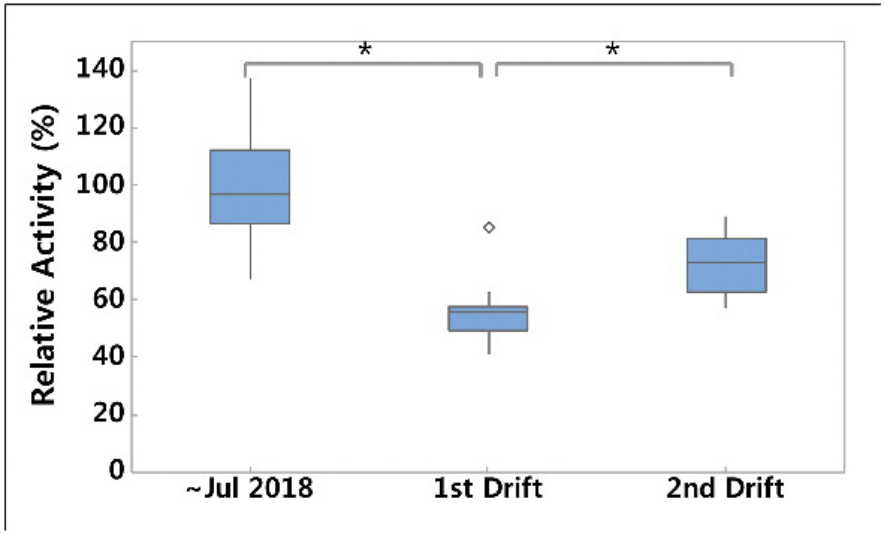
The mean can change over time - Example 3

Trastuzumab reference medicine





Example demonstrates the possibility that strict requirements for equivalence testing of means would be a moving target which could be misused by reference medicine manufacturer to fend off biosimilar competition

Reference: derived from Kim et al. Mabs, 2017; 9. 704-714

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Role of statistical approaches for comparing quality attributes

- Every statistical approach requires prerequisites, i.e. statistical assumptions need to be met
- Equivalence testing for means is of limited value in biosimilar assessments
  - The mean can change over time
  - Strict requirements for equivalence of means bare the risk to falsely reject true biosimilars
- Statistics help to flag differences in quality attributes
- Minor differences in quality attributes can be acceptable if they are found to be clinically meaningless

Appropriate use of statistics may support comparability exercises but cannot serve to set pass/fail criteria for the regulatory conclusion of biosimilarity or comparability following a manufacturing change

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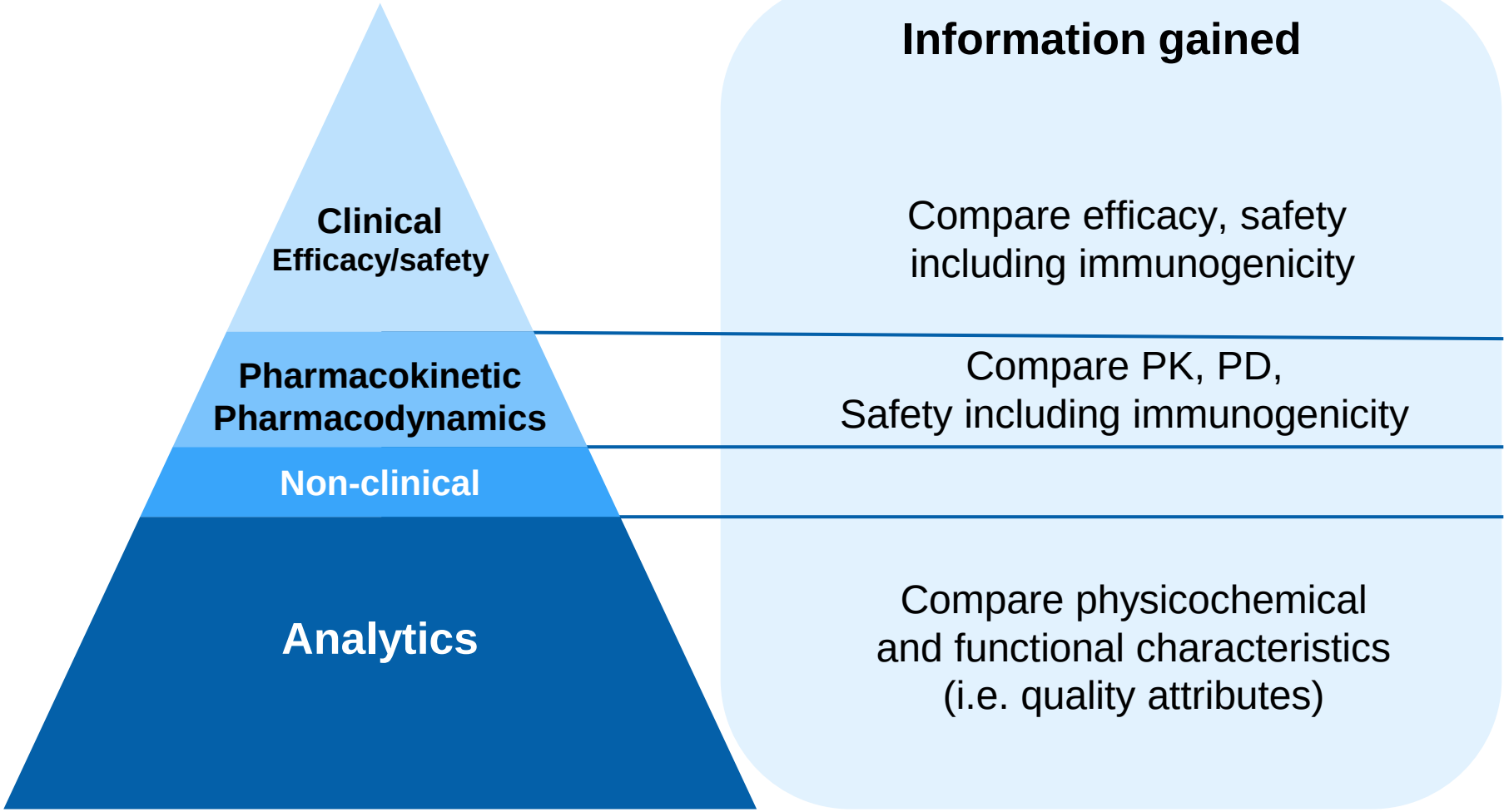
The way forward in biosimilar development



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Thank you

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