BIOSIMILARS – manufacturing and quality requirements

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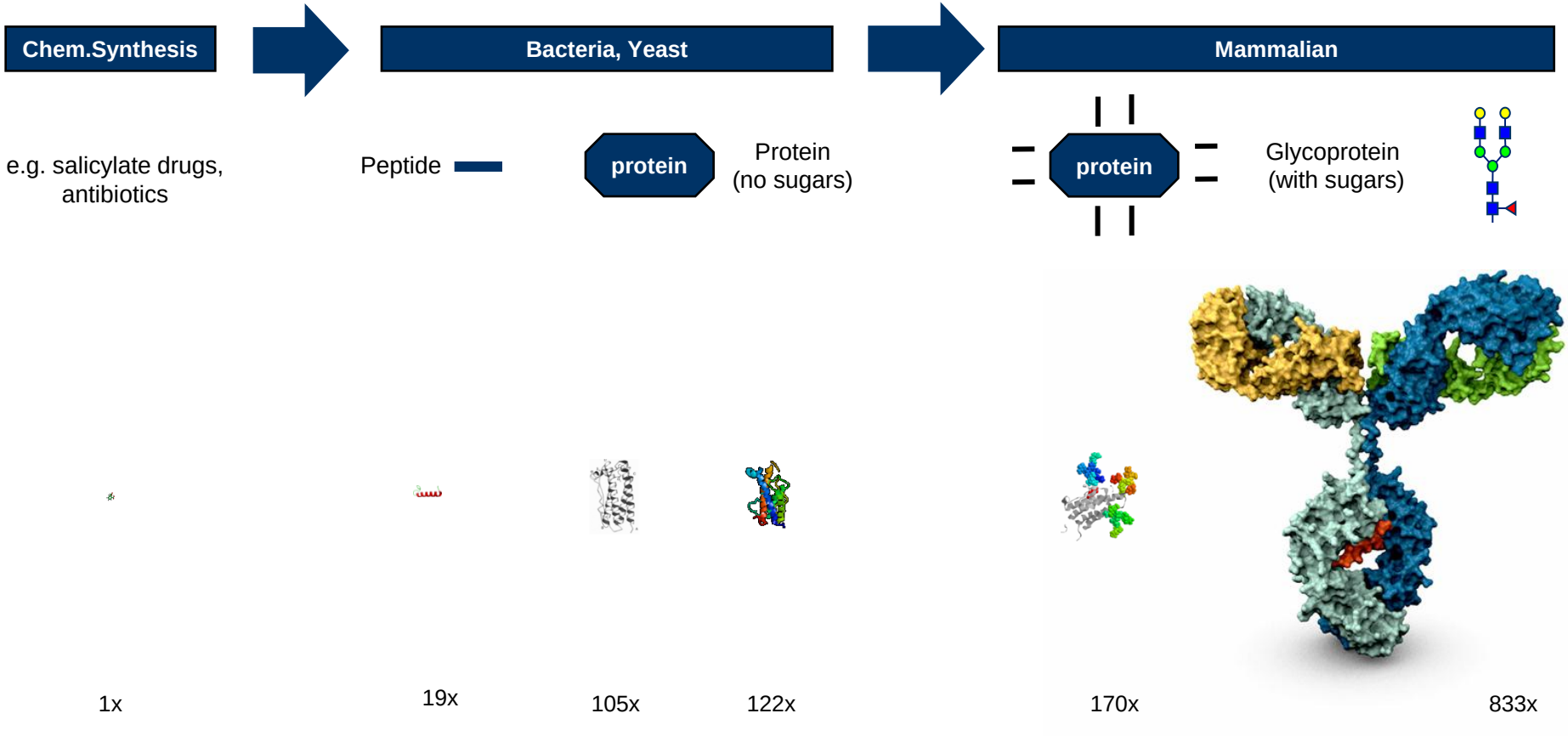
Biologics are more complex than small molecules…



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…and are produced from living organisms

Modify host cells (e.g., bacteria, mammalian yeast) to produce recombinant proteins

Grow cells under controlled conditions (fermentation)

Extract, refold, purify (downstream) – generate drug substance

Formulate to stable finished drug product (vial, syringe, cartridge)

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What is a biosimilar (or follow-on biologic)?

Overview	• **Successor to a biologic** medicine that has lost exclusivity • **Not a simple generic** due to complexity: size, structure and manufacturing
Regulatory definition	• **A biologic approved via a stringent regulatory pathway** demonstrating comparability
Comparability approach	• **Highly analogous structure** (via robust analytical characterization) • **Comparable quality, safety and efficacy** (via clinical trials)

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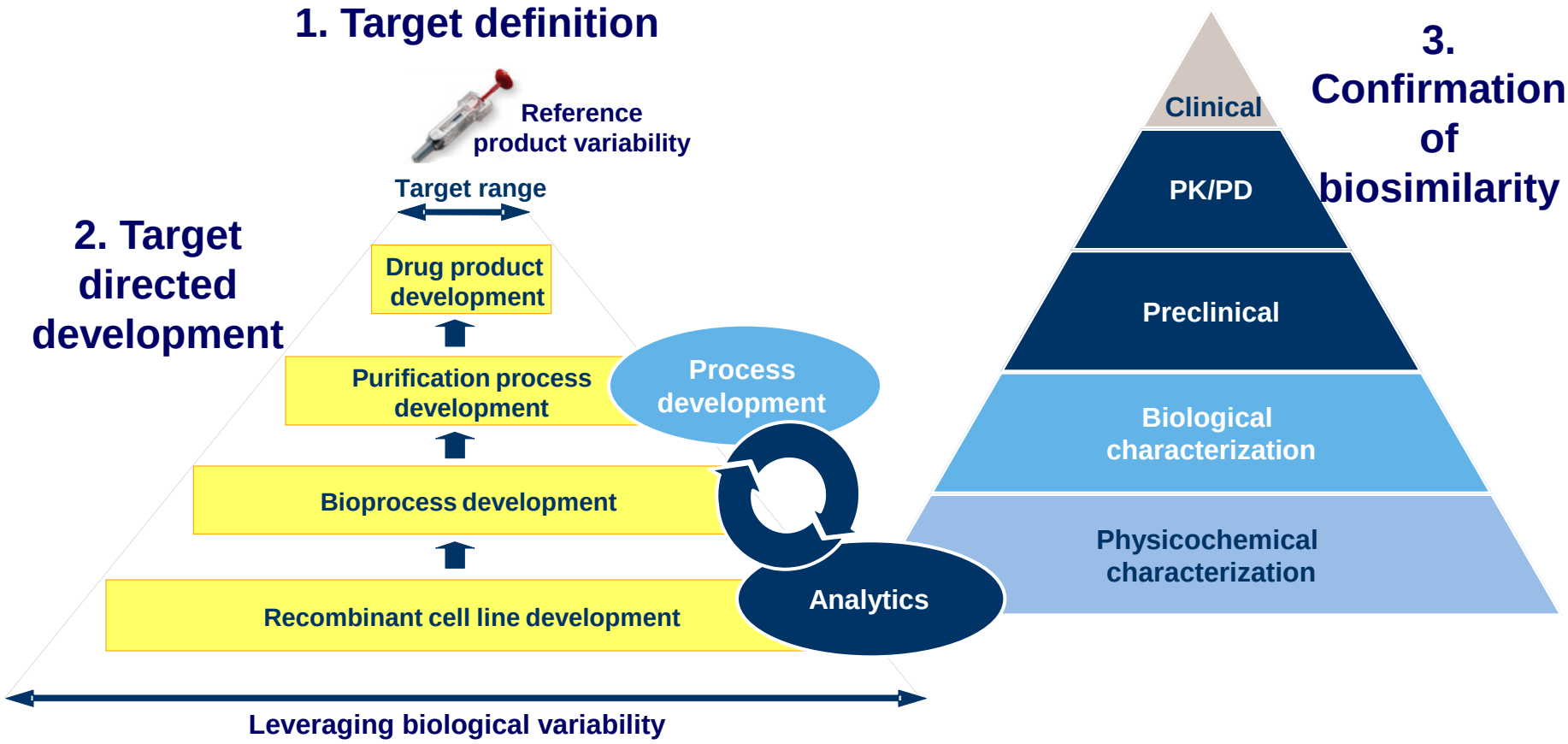
Biosimilar development needs more time and budget, and is more complex than standard Gx development

	Generics	Biosimilars
Costs	US$ 2 – 3m	US$ 100 - 250m
Time to market	2 – 3 yrs	7 – 8 yrs
Clinical	Bioequivalence studies in healthy volunteers	Phase III pivotal studies in patients
Post approval	Pharmacovigilance (PV)	Phase IV studies Risk mgmt. plan (incl. PV)

Source: Sandoz analysis

Note: All pictures are the property of the respective owner

Biosimilar mAbs must be systematically engineered to match the reference product



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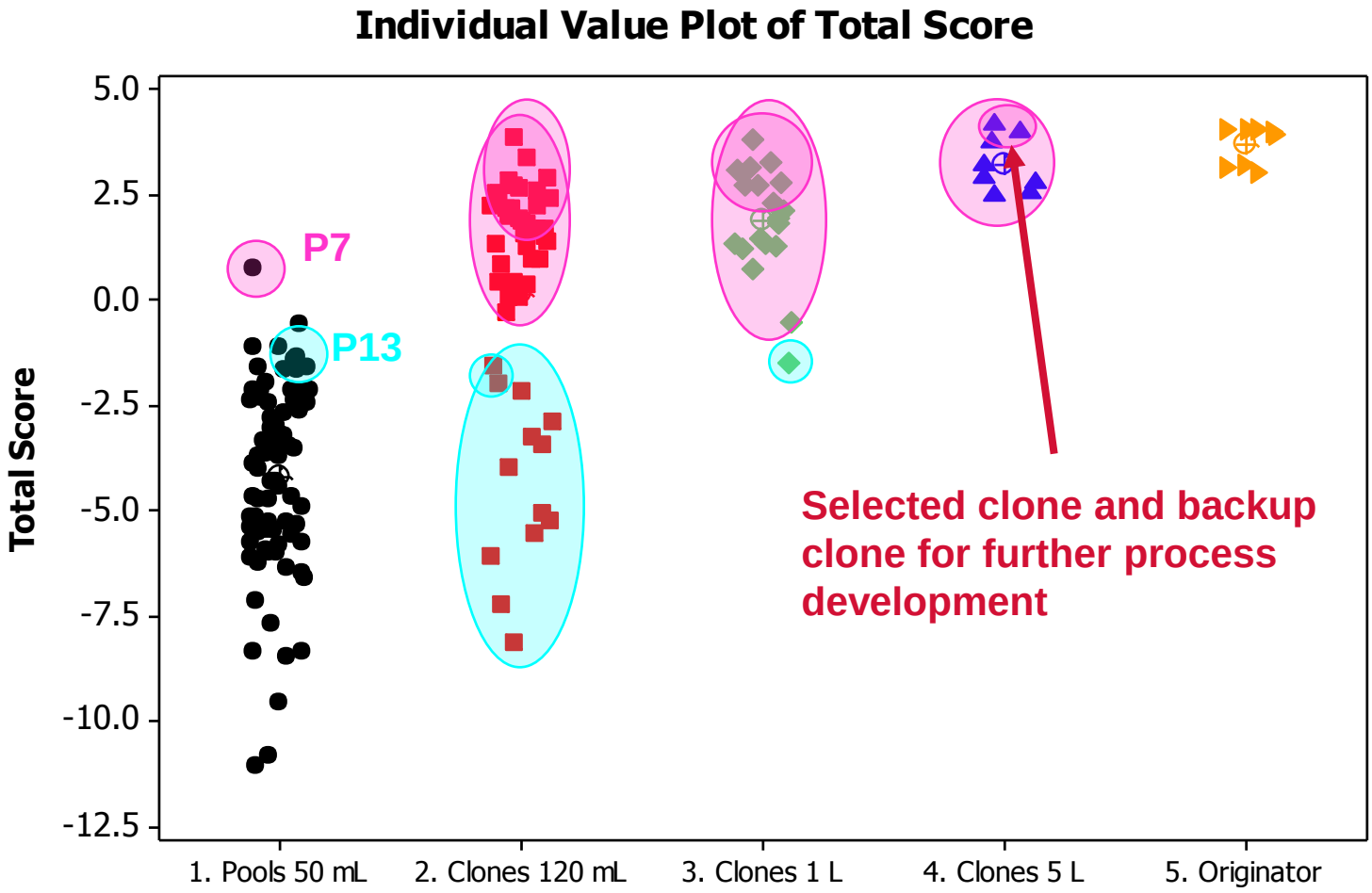
Clone selection case study: Targeting originator



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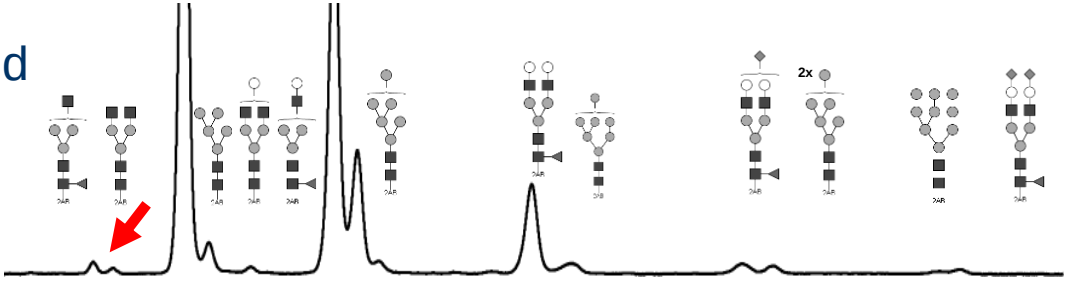
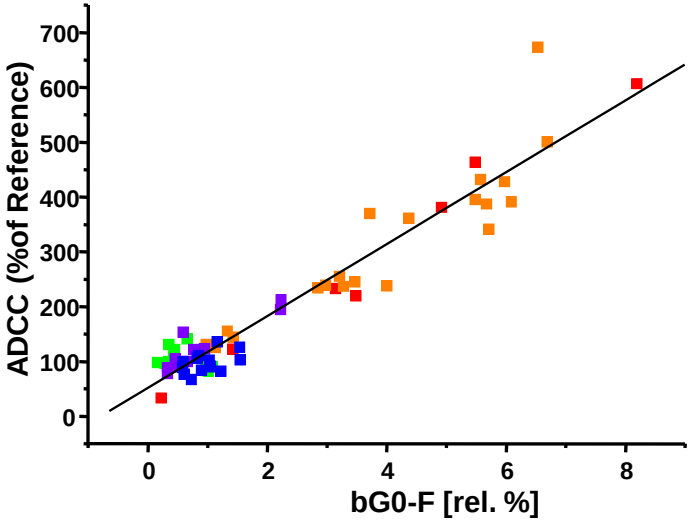
Example for Quality by Design: Attention to detail is essential...

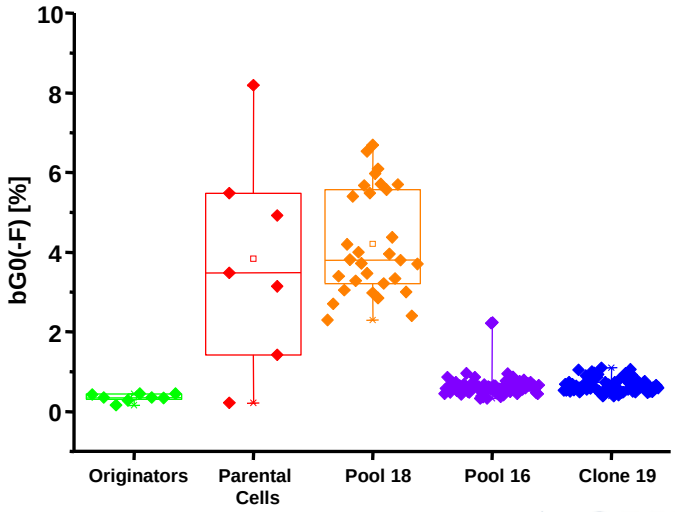
Characterization of mAb glycosylation heterogeneity

High resolution identification and quantification of major (G0,G1,G2) and minor glycan structures
(down to a level of 0.1 rel.%)



Targeting ADCC activity and fucosylation by clone selection





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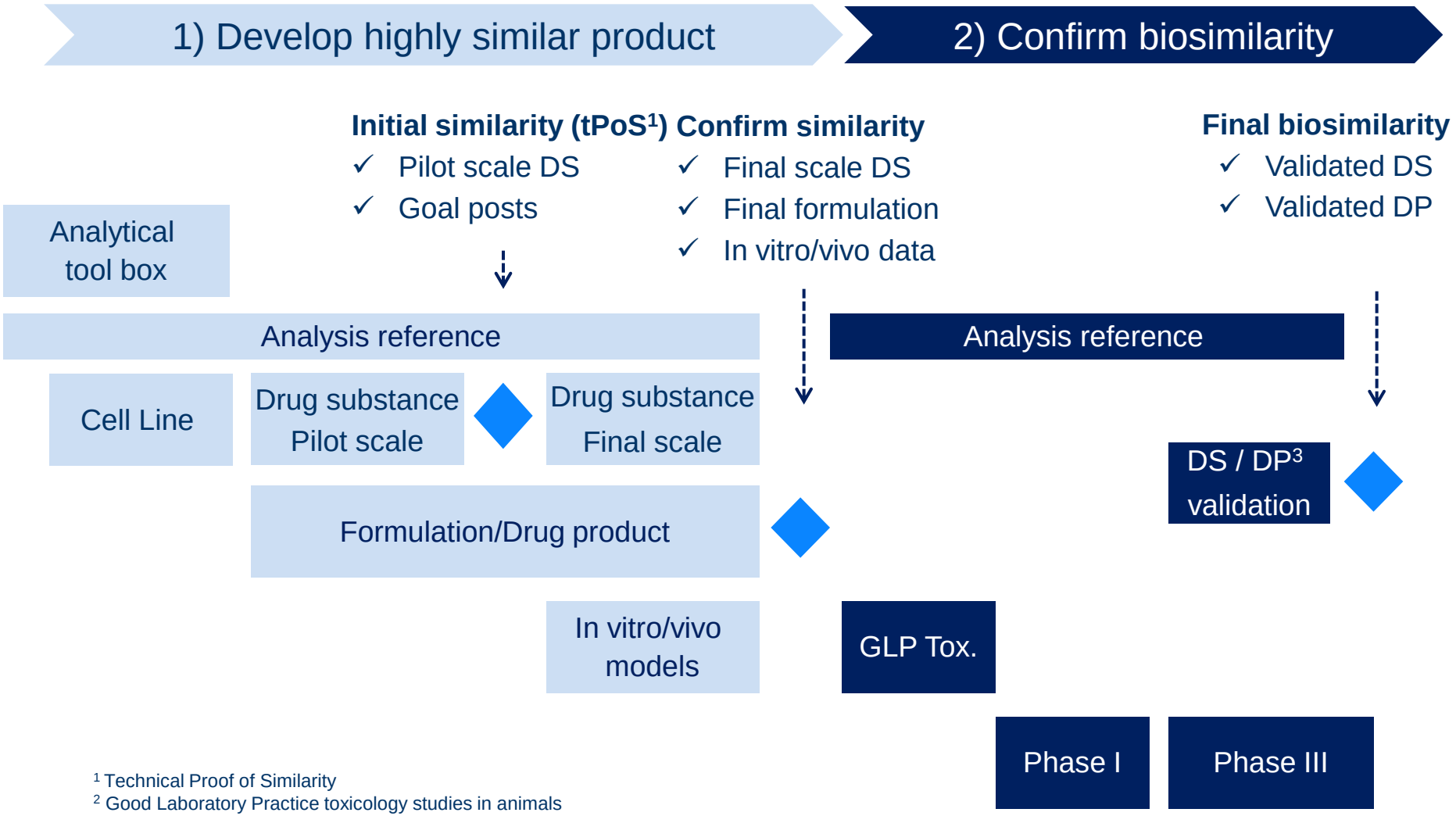
After development of a highly similar molecule, similarity is confirmed by clinical studies



[1] Technical Proof of Similarity
[2] Good Laboratory Practice toxicology studies in animals
[3] Drug substance / drug product

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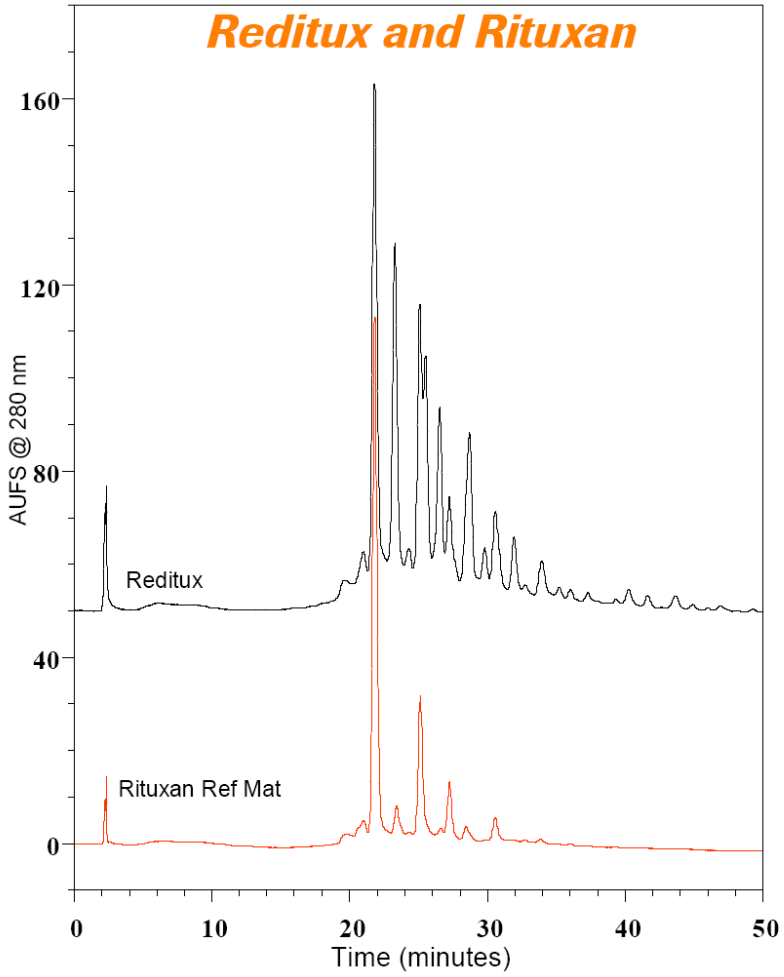
...and follow-on biologics that do not fulfill these high standards are not biosimilars and will not be approved in the EU



Comparison by Cation Exchange Chromatography

- Higher host cell protein content
- Content of aggregates not comparable
- Charge distribution not comparable
- Glycosylation not comparable
- ADCC effector function not comparable
- Clinical data: Only PK/PD study in 17 patients

Source: Mike Doherty, Global Head Regulatory Affairs, Roche Pharmaceuticals, at Roche Investor Day 2010, March 18, 2010, see http://www.roche.com/investors/ir_agenda/rid_2010.htm?track=8 and www.roche.com/irp100318_md.pdf

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Today's analytical science provides a full understanding of the structure of even a mAb...

Attributes:

- Primary structure
- Mass
- Disulfide bridging
- Free cysteines
- Thioether bridging
- Higher order structure
- N- and C-terminal heterogeneity
- Glycosylation (isoforms, sialic acids, NGNA, fucosylation, alpha gal, site specific)
- Glycation
- Fragmentation
- Oxidation
- Deamidation
- Aggregation

Proteins can be well characterized at least up to the complexity of monoclonal antibodies

- Primary structure determined from recombinant DNA sequence and fully accessible to analytical verification
- Set of orthogonal analytical methods available to characterize the identity and amount of related variants with high sensitivity
- Glycosylation profile can be comprehensively determined with regard to identity and content of individual glycans with high sensitivity
- Accurate and relevant bioassays for pivotal biological functions available

Methods e.g.:

- MS (ESI, MALDI-TOF/TOF, MS/MS)
- Peptide mapping
- Ellman's
- CGE
- SDS-PAGE
- CD
- H-D exchange
- FT-IR
- HPLC
- HPAEC
- IEF
- 2AB NP-HPLC
- SE-HPLC
- FFF
- AUC
- DLS
- MALLS

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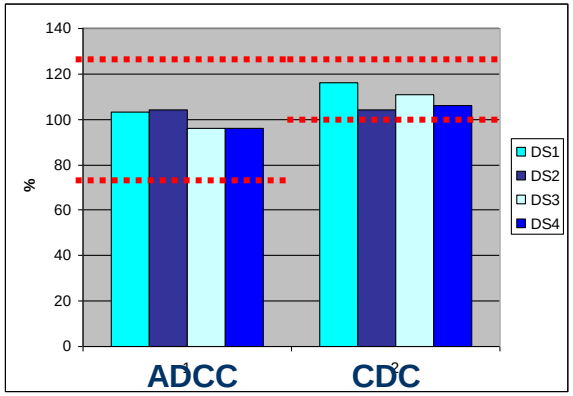
Challenges of biosimilar development

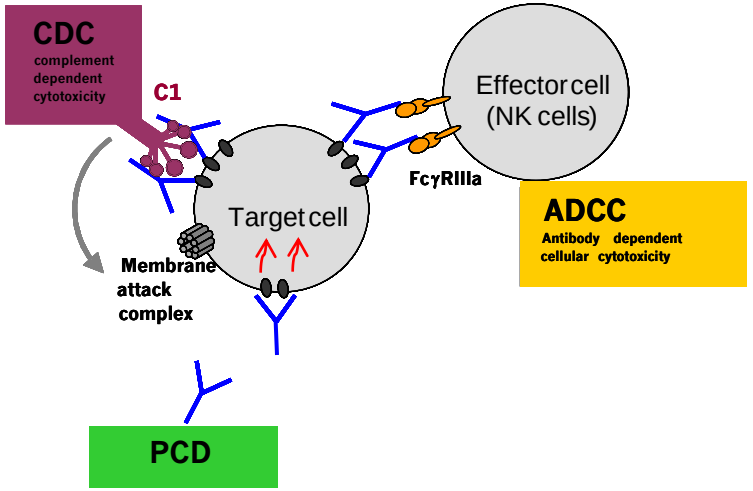
- Development approach different from generics but also from new biotech drugs
  - Iterative process
  - Limits of reference product target ranges

- Heavy upfront investment in process development and characterization as well as analytical development
  - Many key developments before the first clinical trial (vs. conventional pharma model after proof-of-concept, before pivotal phase 3 trials)
- Extensive analytics very early in development
  - Analytical methods sensitive to detect differences and similarities
  - Including bioassays

TPoS of a Biosimilar mAb: Biological Characterization

- **Bioassays**
  - Target binding – comparable; ADCC - comparable
  - CDC – comparable; Apoptosis - comparable





- **Binding assays (SPR)**
  - FcγR (RIA, RIIA, RIIB, RIIIA^{158F}, RIIIA^{158V}, RIIIB) - comparable
  - FcRn - comparable

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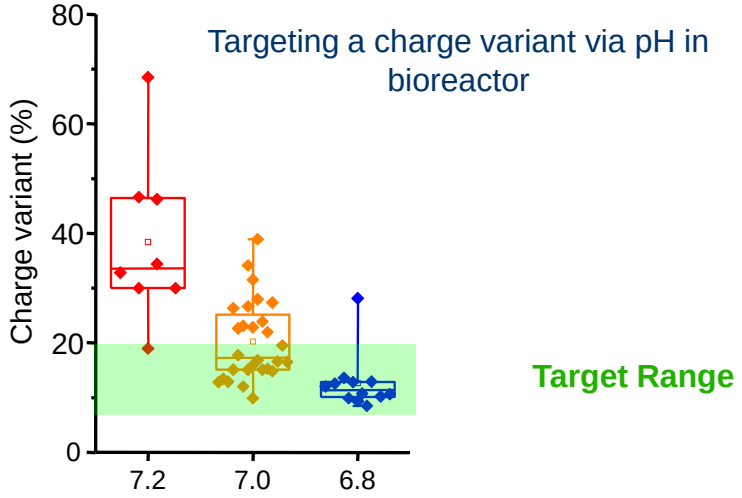
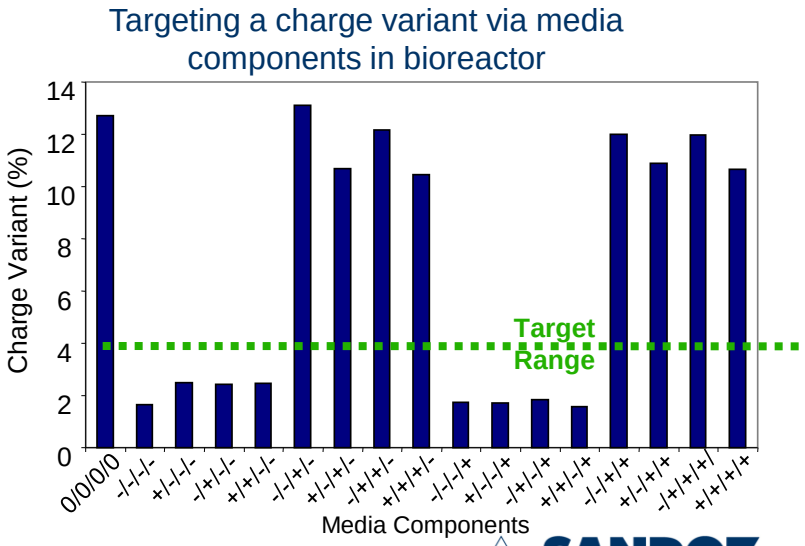
Challenges of biosimilar development ctd.

- Manufacturing: targeted for biosimilar product while balanced for COGS
- Understanding of criticality of quality attributes as well as process parameters
- How close is close enough?

Target directed process development
Example: Adjusting mAb variants in the bioreactor

- Charge-variants are typical product-related variants for mAbs:
  - acidic variants (e.g. de-amidation of Asn)
  - basic variants (e.g. amidation of Pro)
  - pyroglutamate/Gln at N-terminus
  - Lys-variants at C-terminus
  - mAb fragments
- Charge-variants can be adjusted in the bioreactor by optimization of
  - process parameters
  - media components





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Challenges of biosimilar development ctd.

- Manufacturing: targeted for biosimilar product while balanced for COGS
- Understanding of criticality of quality attributes as well as process parameters
- How close is close enough?
- Drug product: formulation and packaging to mirror the reference product
- Global reference product
- Shifts in reference product attributes
- Biosimilarity exercise as extreme form of comparability exercise (same scientific principles)

Biosimilars are produced under the same stringent cGMP requirements

... as innovative Biopharmaceuticals:

- Quality-by-Design based process development
- Quality Assurance approved documentation
- State-of-the-art manufacturing facilities
- Quality Assurance systems to detect deviations, out-of-specification and out-of-trend results

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Conclusions

- Biosimilars are important for improved patient access to modern biopharmaceuticals

- A targeted approach is key for successful development of biosimilars

- Biosimilar development faces big manufacturing, process development and analytical challenges - some of them common for any biopharmaceutical, some of them specific for biosimilars, but are surmountable provided a proper and state-of-the-art development of Biosimilars is done

Thank you!

Questions?

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