Making Medicines Affordable

High Level Perspective of the Biosimilars Industry

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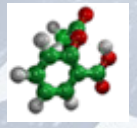
JOERG WINDISCH, Ph.D.

Chair, EGA European Biopharmaceuticals Group (EBG), and
Global Head Technical Development, Sandoz Biopharmaceuticals

EGA greatly appreciates the two new guidelines on biosimilar mAbs and mAb immunogenicity testing

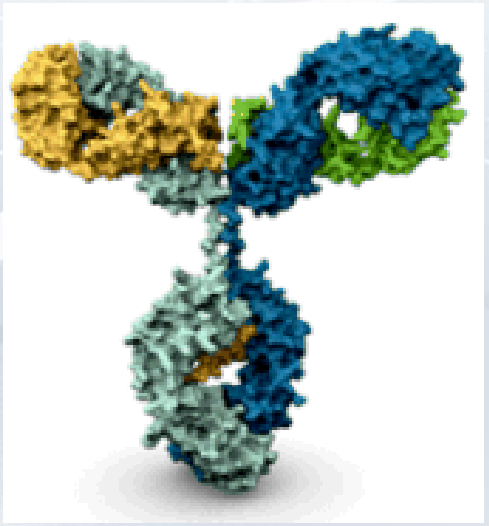
- Ensure patient safety and efficacy
- Science based
- Take into account what is already known about mAbs in general and reference products
- Allow novel scientific approaches

mAbs are complex...



Aspirin®

Calcitonin

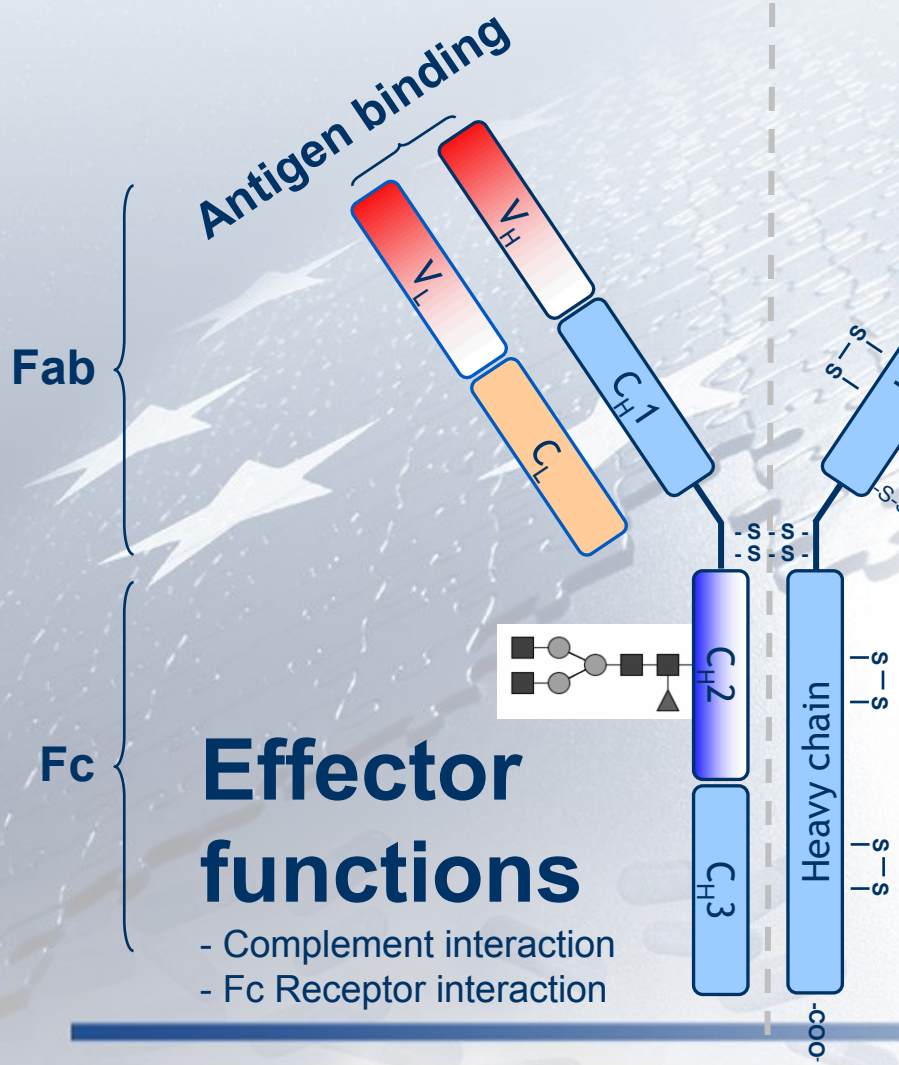


Monoclonal Antibody

small molecule	peptide	complex biologic
Molecular weight = 180 Daltons 0 amino acids	Molecular weight = 3,455 Daltons ~ 32 amino acids -w/o host cell modifications -Produced synthetically or in yeast, bacteria	Molecular weight = 150,000 Daltons ~ 1300 amino acids -w/ host cell modifications (glycosylation etc.) -Produced in mammalian cells

…but can be thoroughly characterised today

Biological characteristics



Effector functions

- Complement interaction
- Fc Receptor interaction

Physicochemical characteristics

N-terminal heterogeneity
Pyroglutamate formation
Other modifications

Amino acid modifications
Deamidation, Oxidation, Glycation, Isomerization

Fragmentation
Cleavage in hinge region, Asp-Pro

Oligosaccharides
Fucosylation, Sialylation, Galactosylation,...

Disulfide Bonds
Free thiols, disulfide shuffling, thioether

C-terminal heterogeneity
Lysine processing, Proline amidation

Use of orthogonal methods provides understanding of the overall picture

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

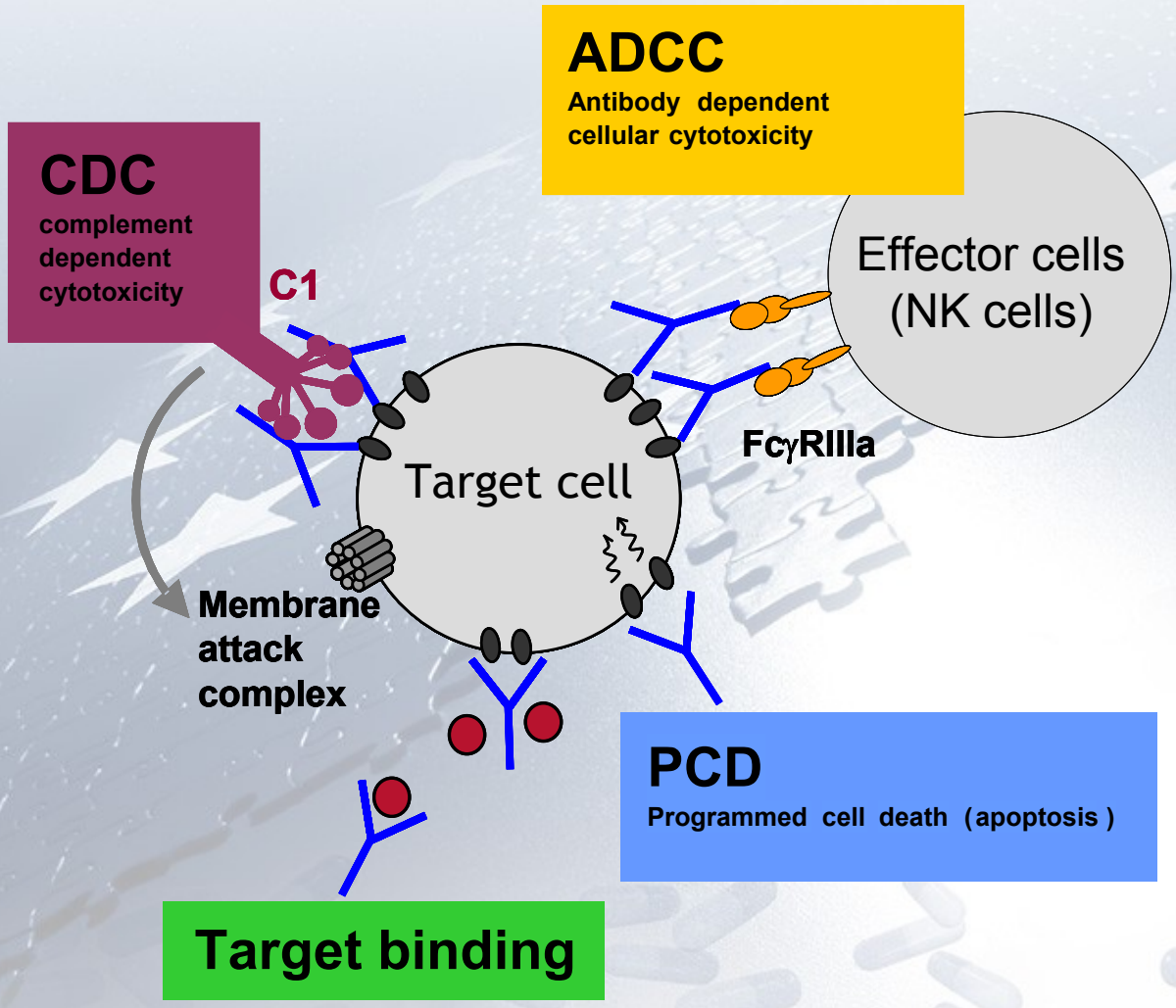
Proteins can be well characterized at least up to the complexity of monoclonal antibodies

- 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

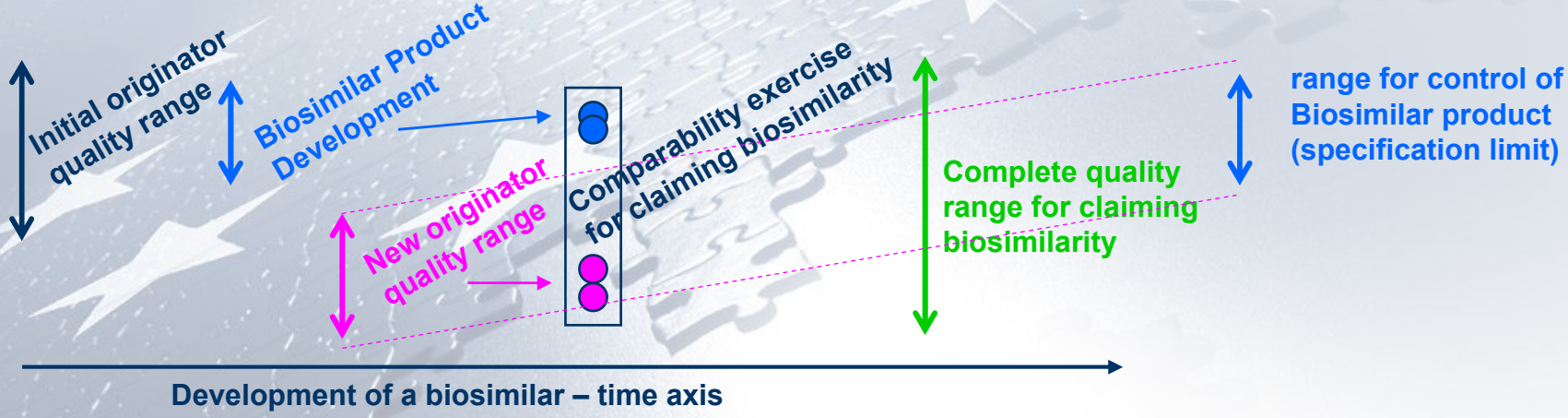
Functional similarity is demonstrated by multiple *in vitro* bioassays



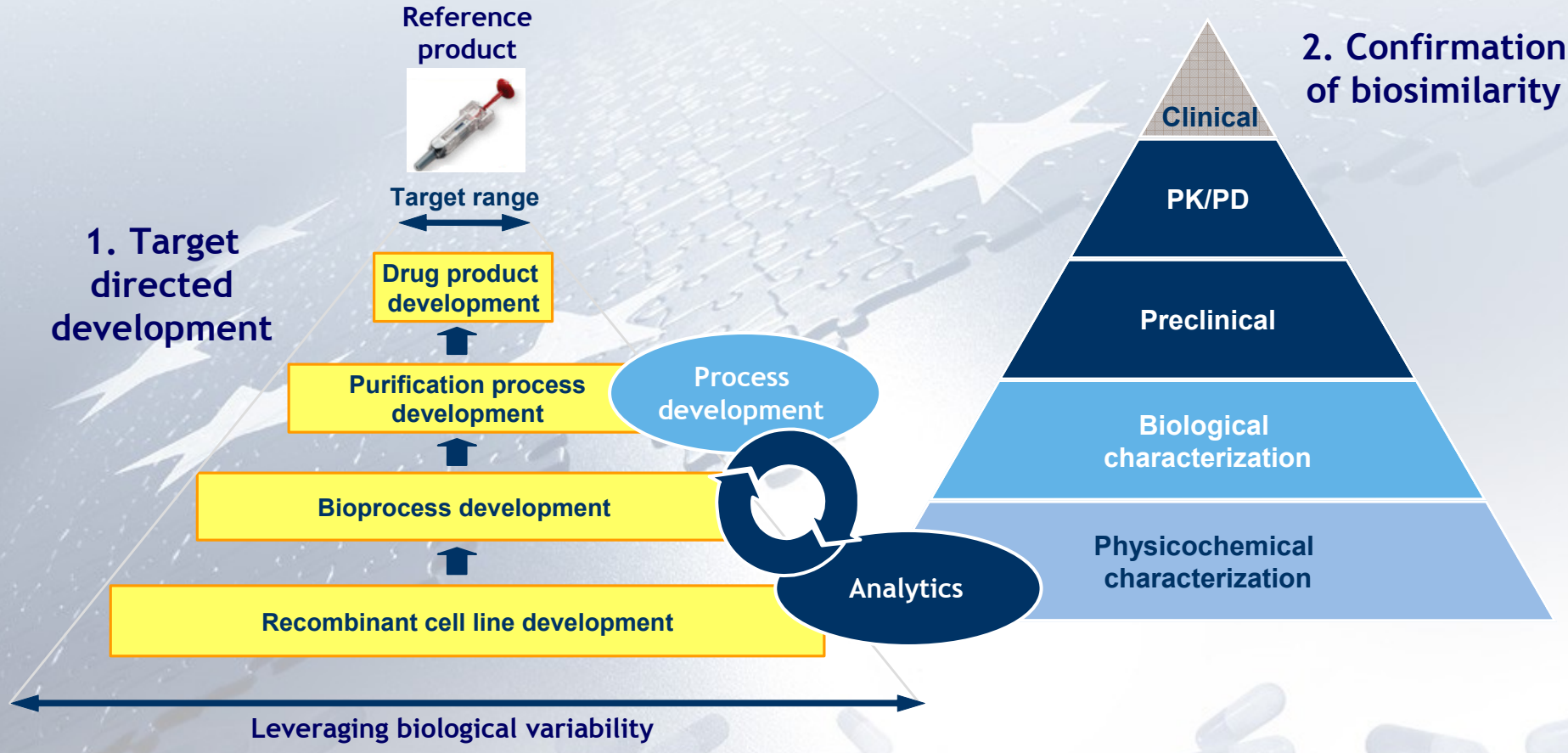
Methods e.g.:

- Cellular binding assay
- SPR binding assay
- Cell based ADCC assay
- FcγR binding
- Cell based CDC assay
- Cell based apoptosis assay
- FcRn binding

Variability in reference products is significant and sets the goal posts



Target directed development and confirmation of biosimilarity



Biosimilar mAb guideline: What is great

- Excellent guidance document overall
- Bases development on similarity as established analytically and by *in vitro* biological assays
- Animal studies only as necessary
- Stresses importance of human PK/PD studies for demonstrating biosimilarity and extrapolation
- Clinical development should focus on demonstration of biosimilarity, not patient benefit *de novo*
- Allows alternative and earlier endpoints
- Allows extrapolation of indications

Biosimilar mAb guideline: What we ask EMA to reconsider

- It should not be required for *in vitro* biological studies to « cover all functional aspects of the mAb even though some may not be considered necessary for the mode of action in the clinic »
- It should be allowed, if justifiable, to perform the human PK study in parallel to the safety/efficacy trial
- There should be flexibility to diverge from the use of the « most sensitive model » in safety/efficacy trials if justifiable
- It should be allowed to use non-inferiority designs in safety/efficacy trials in certain circumstances
- Post-authorisation follow-up should not exceed routine pharmacovigilance

mAb immunogenicity guideline: What is great

- Based on cutting edge knowledge about immunogenicity testing
- Comprehensive and science based
- Ensures patient safety

mAb immunogenicity guideline: What we ask EMA to reconsider

- Biosimilars should not be treated as separate class of mAbs
- Scientific approach to immunogenicity assessment of biosimilars should be analogous to immunogenicity assessments after manufacturing process changes
- The guideline should be aligned with biosimilar mAbs guideline to prefer *in vitro* non-clinical studies over animal studies also for immunogenicity assessment whenever scientifically reasonable
- We would recommend to improve readability and user-friendliness a bit

Summary

- We appreciate the high quality of the two draft guidelines
- We ask the BMWP and EMA to reconsider a few elements in the interest of broadening patient access
- We look forward to science-based and constructive discussions in today‘s workshop...