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# The EGA's Perspective on Biosimilar Products

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- **Definition**
- **Basic concepts**
- **Global biosimilar development**
- **Status of biosimilar products in Europe**
- **The next step - monoclonal antibodies**
- **Conclusion**



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# Definition





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# What is a Biosimilar Product?

- A biosimilar medicinal product is a successor to a biological medicinal product for which patent protection no longer applies
- Manufactured by recombinant DNA technology (insertion of gene into the host cell to produce the protein)
- Comparable with the selected comparator biomedicine(\*) in terms of quality, safety and efficacy
- The biosimilar product is usually approved for the same indications as the comparator biomedicine given that they share the same mode of actions

(\*) EU Terminology: reference product

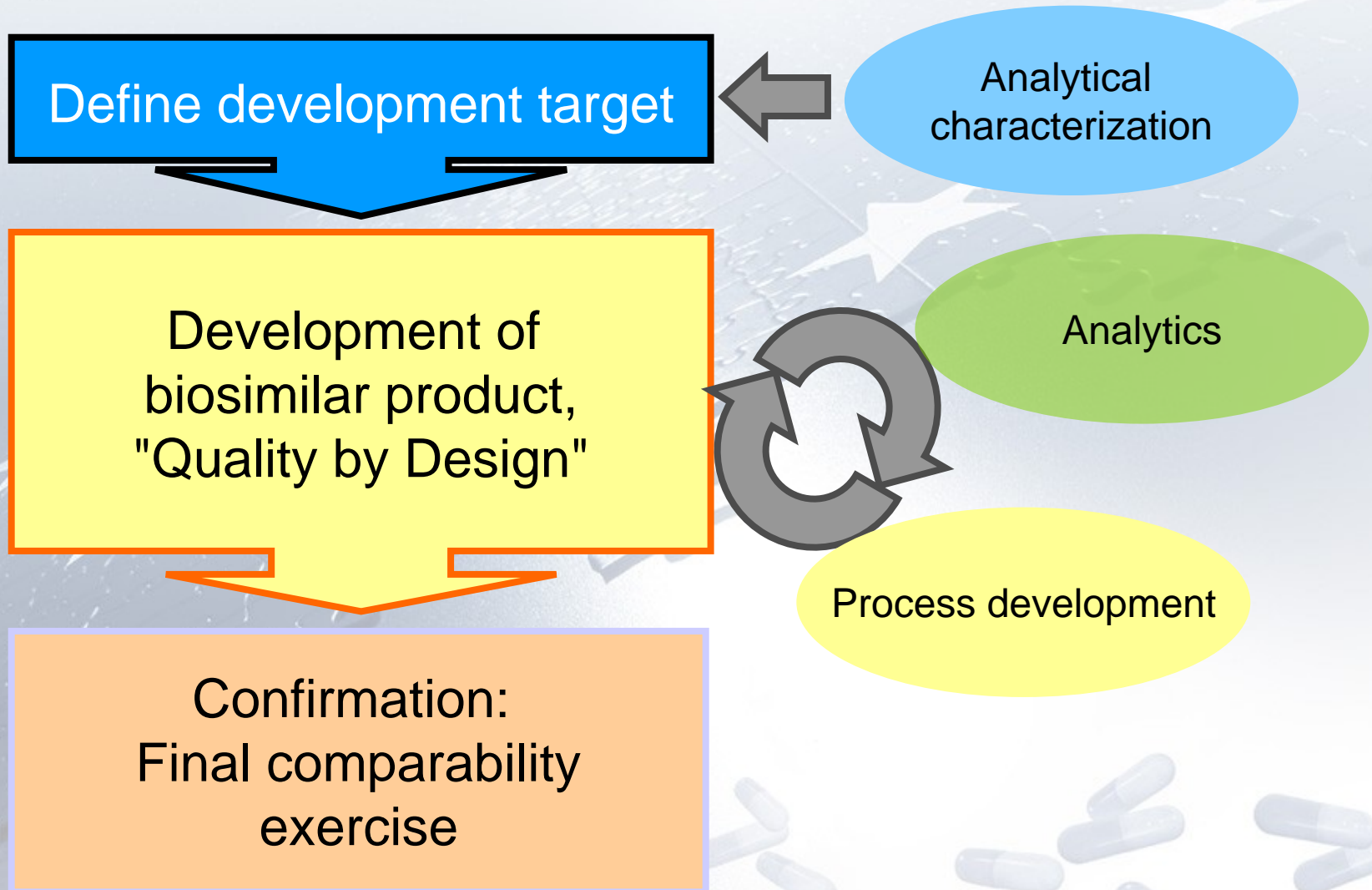


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# Basic Concepts



# Development of a Biosimilar Product Following a Target Directed Approach





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# Quality by Design

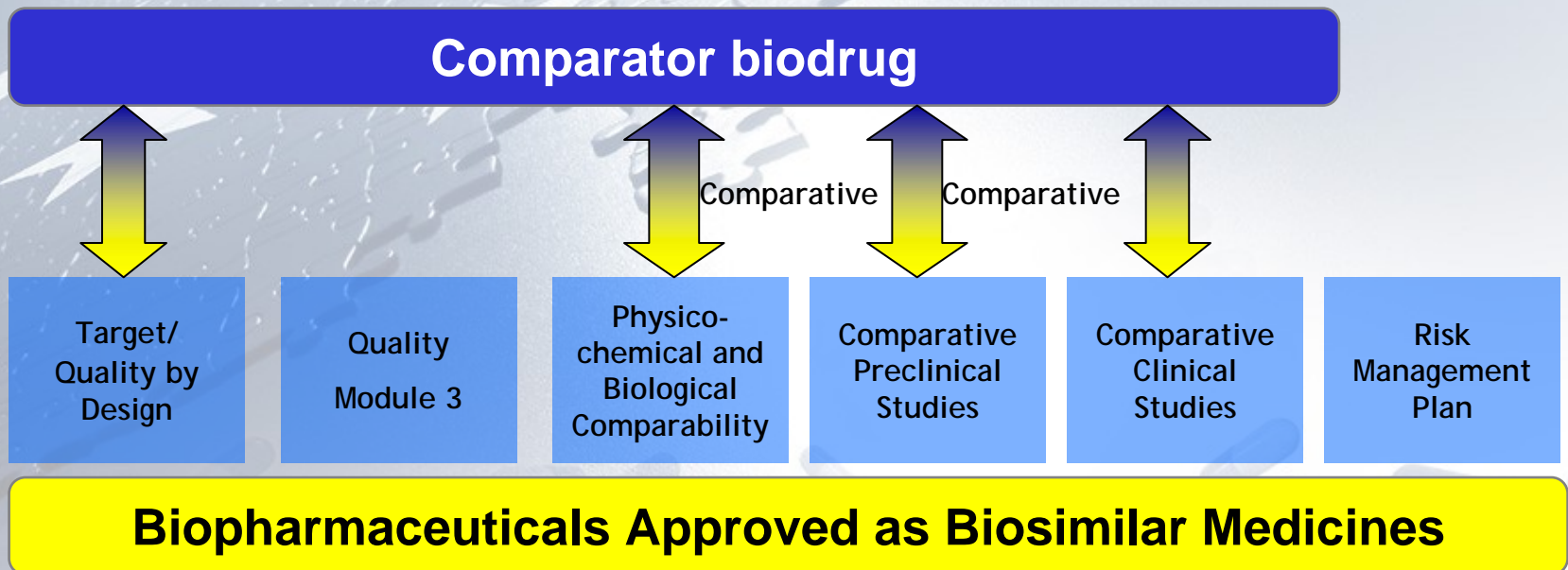
- **Manufacturing process is pro-actively designed to achieve a product equivalent to the comparator biodrug (quality, safety & efficacy)**
  - Extensive characterization of reference product (multiple batches)
  - Broad set of orthogonal state-of-the-art analytical tools
  - Accounting for formulation, packaging materials, etc.
  - In vitro biological testing, in vivo PK/PD studies, clinical trial
- **Continuous feedback between process development and high performance analytical techniques result in the required specific selection of**
  - Cell line
  - Raw materials, media
  - Upstream and downstream process parameter
  - Control of critical variables
  - Formulation, primary packaging, delivery system

# Biopharmaceuticals Approved as Biosimilar Medicines have been Compared Thoroughly

The development of a biosimilar medicine requires a complete product and process development

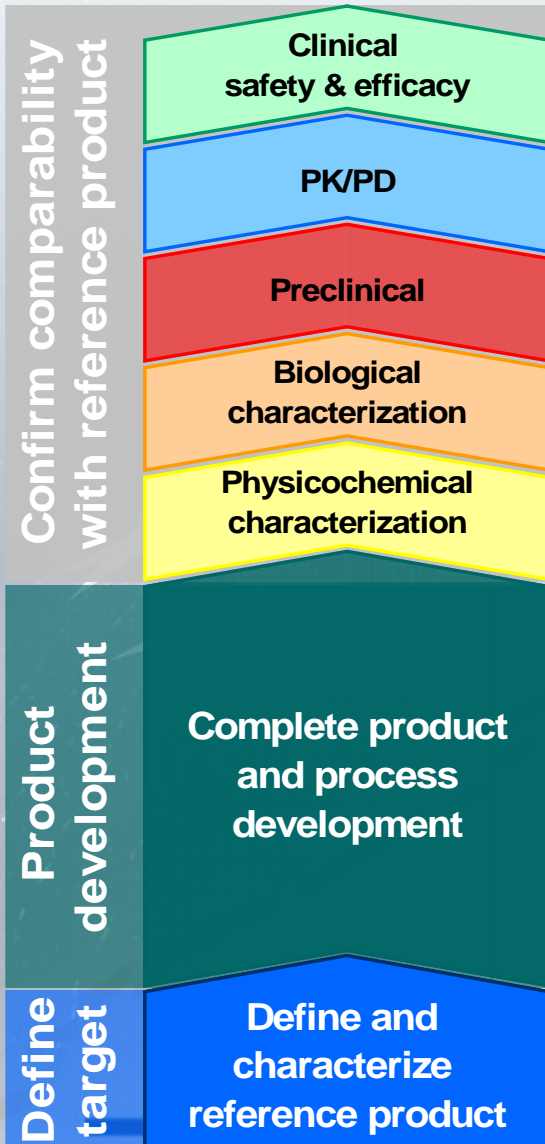
**PLUS**

comparative testing at all stages of in order to obtain approval by the European authorities (EMA, CHMP, EC)





# The Comparability Exercise - the Core Element in the Biosimilar Product Development



The comparability with the comparator biomedicine must be demonstrated at all levels of product development

A biosimilar product is designed to meet the criteria of the comparator biomedicine with regards to quality, safety and efficacy.

This rigorous comparability exercise qualifies Biosimilars for therapeutic interchange



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# How Close is Close Enough?

- The criteria for the comparison of the biosimilar candidate and the comparator biologic are based on
  - Understanding batch-to-batch variability of the comparator biologic
  - Classification of the product variants into product-related substances or impurities (ICH Q6B)
  - Level of understanding the relevance of subtle differences on safety/efficacy (ICH Q5E)
  
- The manufacturing process for the biosimilar is systematically designed to meet the required comparability criteria



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# Global Development of Biosimilar Medicines



# Global Development of Biosimilars

## What is the Issue?

- The Japan draft guideline, the European and probably also future US legislation will require the **use of a comparator biodrug authorised in their jurisdiction**
- This would require the performance of **separate development programs** for each country/region which is **unnecessary, unethical** (duplication of preclinical and clinical studies) **and uneconomical**
- The **development** of biosimilar products is **expensive**

# Global Development of Biosimilars

## What is the Issue?

- **Comparator biodrugs** are **often the same** or highly similar in different countries, even though licensed under different jurisdictions
  - Often, **documentation** is available in the public domain that the products are the same
  - **Comparability** of comparator biodrugs of one original manufacturer from different highly regulated countries (JP, US, EU) can be clearly established by stringent analytical and functional studies
- Under these premises it **should not be required to duplicate** preclinical and clinical **studies for each country/region**



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# Global Clinical Development

- **Extrapolation of results and conclusions of clinical studies performed in one population to other populations**
  - Evaluate ethnic sensitivity of medicinal product - does it behave differently in different populations?
  - In compliance with ICH E5(R1) "Ethnic Factors on the Acceptability of Foreign Clinical Data"
  - In line with the spirit of the declaration of Helsinki which aims at avoiding duplication of tests and trials on animals and humans



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# Global Clinical Development

## ■ Points to consider

- Pharmacology and Mode of Action
- Diagnostic criteria and indications
- Posology and dose response
- Pharmacodynamics and pharmacokinetics

# Global Development: Stepwise Approach to show Comparability with Comparator Biodrugs

JP	US	EU	Requirements
✓	✓	✓	rigorous physicochemical and biological comparison with comparator biodrug of both regions ↓
✓	✓	✓	appropriate comparative pre-clinical testing with comparator biodrug of both regions in case of physico-chemical differences shown between drugs ↓
✓	✓	✓	rigorous comparative PK/PD clinical studies with comparator biodrug of both regions ↓
✓			comparative clinical studies with comparator biodrug from <u>one</u> region only (against <u>either</u> JP, US, or EP comparator biodrug)



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# Status of Biosimilar Products in Europe





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# EU Biosimilar Approvals

## ■ Approved Substances

- Human Growth Hormone
- Epoetin
- Filgrastim

## ■ 11 Marketing Authorisations





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# The Next Level Monoclonal Antibodies



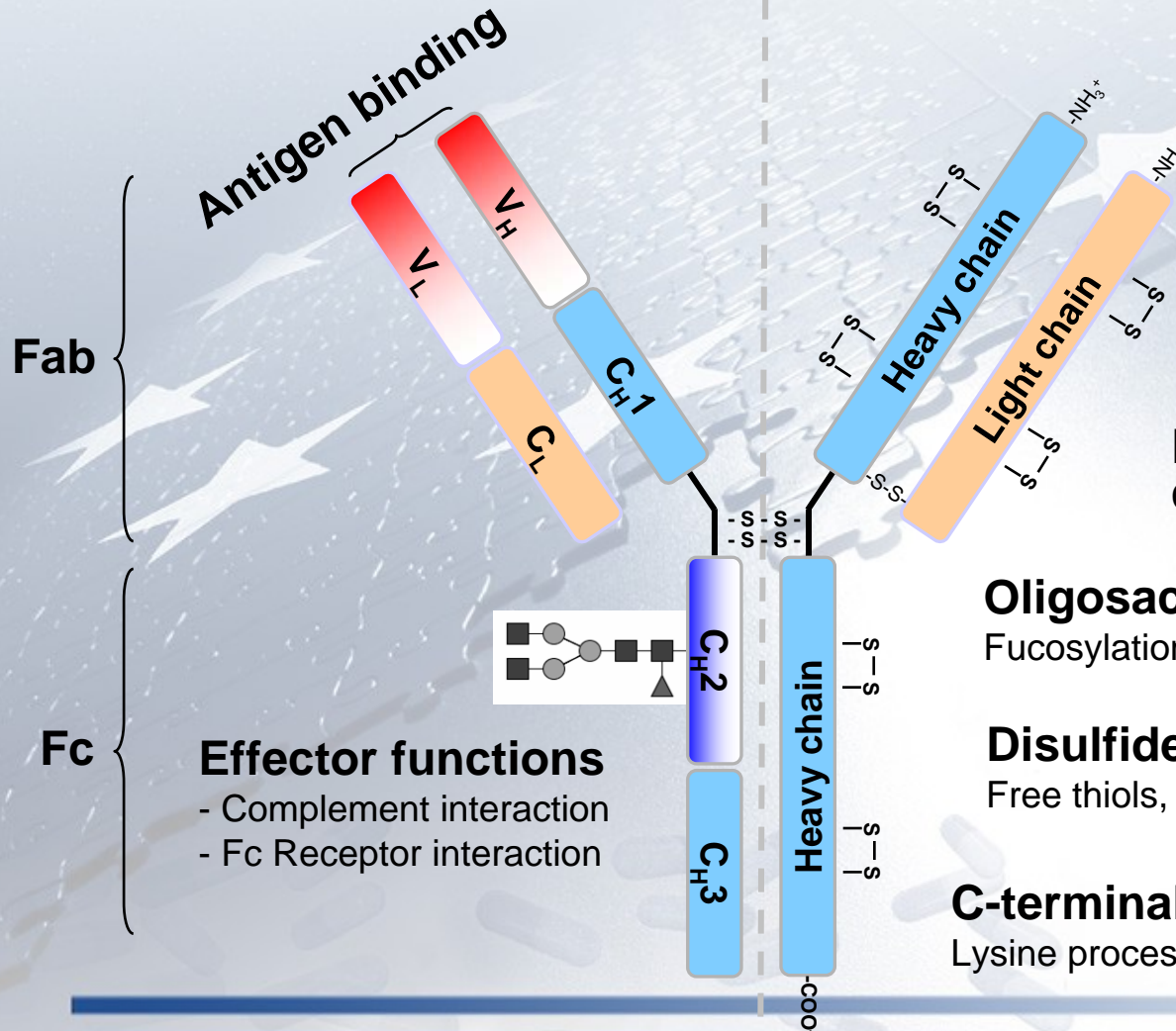


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# The Logical Next Step Monoclonal Antibodies

## Biological characteristics

## 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

### Effector functions

- Complement interaction
- Fc Receptor interaction



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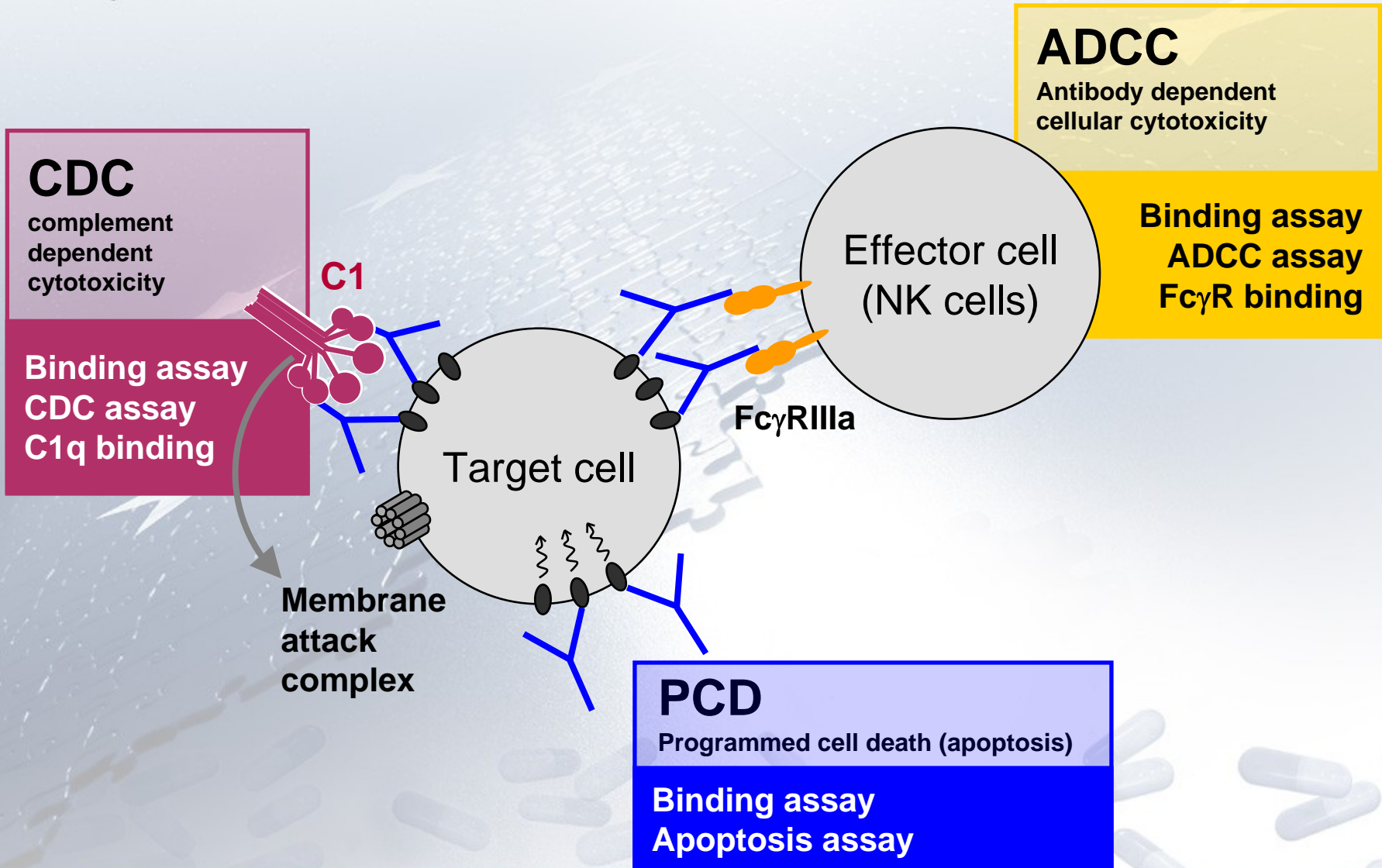
# Physicochemical Characterization of mAbs: Structure, Heterogeneity and Degradation

Molecular Parameter	Attribute	Methods for control and characterization
Primary structure	Sum formula: Mass of light chain, heavy chain and of intact mAb	LC-ESI-MS
	Amino acid sequence	Orthogonal peptide maps with high resolution MS and MS/MS sequencing
	Disulfide bridging	Non-reducing Peptide Map
	Free cysteines	Ellman's, Peptide Map
	Thioether bridging	Peptide map, SDS-PAGE, CGE
Higher order structure	Secondary and tertiary structure	CD spectroscopy, DSC, H-D-Exchange, FT-IR
Glycosylation	Glycan isoforms	NP-HPLC-ESI-MS of 2AB-labeled glycans, exoglycosidase digestion, MALDI TOF/TOF
	Sialic Acids incl. NGNA	NP-HPLC, WAX, HPAEC; RP-HPLC (DMB-label)
	Aglycosylated mAb	CGE, Peptide map
Heterogeneity	C- and N-terminal: $\pm$ Lys, pyroGlu	CEX; Papain-IEX; Peptide Map, RP-HPLC
	Glycation of Lys	Boronate affinity; LCMS; Peptide map
	Oxidation	RP-HPLC; Papain-HIC; Peptide map
	Deamidation	CEX; Papain-IEX; Peptide map
	Aggregation	SEC, FFF, MALLS, DLS, AUC; imaging, particle char.
	Fragmentation at disulfides (HL, H <sub>2</sub> L, H, L) and in amino acid chain (p100, p50)	CGE, SDS-PAGE, SEC, RP-HPLC



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# A Toolbox of Bioanalytical Methods Addresses Possible Mechanisms of Action for a mAb





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# Conclusion





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# Conclusions

- Biosimilar Medicines are a reality in the EU
- Multiple biosimilars are being used safely and providing access to competitively priced products to numerous patients
- Thorough demonstration of comparability provides the scientific basis for interchangeability
- Current science allows development of a diverse portfolio of biosimilar products, including monoclonal antibodies
- Global biosimilar development is possible based on sound scientific principles and should be enforced by regulatory pathways



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**Thank you for your attention**



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# Main Acronyms Used

- EGA European Generic medicines Association
- EMEA European Medicines Agency
- CHMP Committee for Medicinal Products for Human Use
- EC European Commission
- EU European Union
- RMP Risk Management Plan
- ICH International Conference on Harmonisation
- JP Japan
- US United States of America