Making Medicines Affordable

EUROPEAN GENERIC MEDICINES ASSOCIATION

Making Medicines Affordable

EGA's Perspective on Biosimilar Products

Martin Schiestl, PhD
Head Analytics and Pharmaceutical Development
Biopharmaceutical Operations
Sandoz
On behalf of the European Generic medicines Association

PMDA, 3rd International Symposium on Biologics
17 February 2009, Tokyo

Making Medicines Affordable

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

Making Medicines Affordable

Definition

What is a biosimilar product?

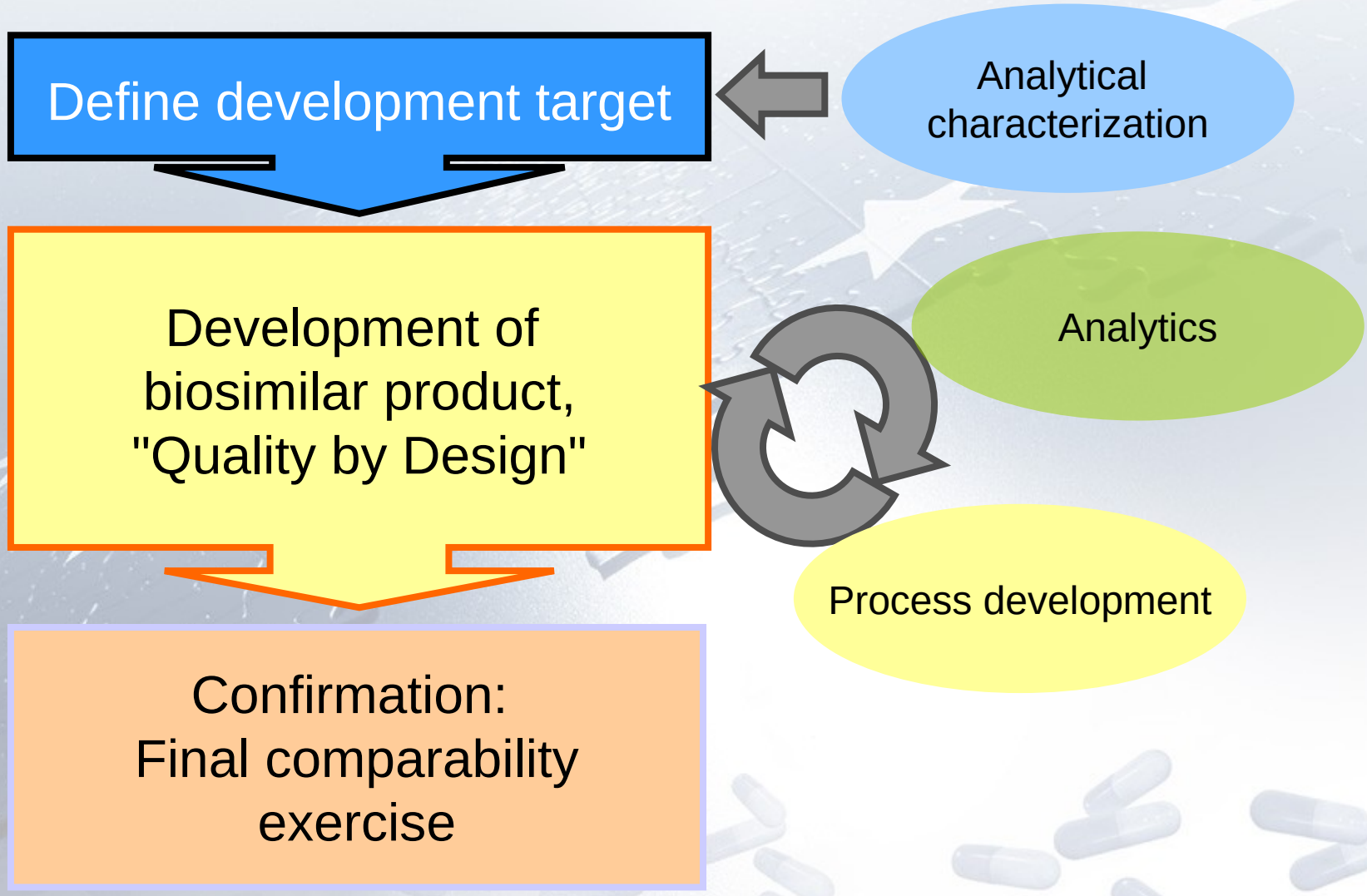
- A biosimilar medicinal product is a successor to a biological medicinal product for which patent protection no longer applies
- Manufactured by recombinant DNA technology (insertion of gene into the host cell to produce the protein)
- Comparable with the selected comparator biodrug(*) in terms of quality,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

(*) EU Terminology: reference product

Making Medicines Affordable

Basic Concepts

Development of a follow-on product following a target directed approach



Quality by Design

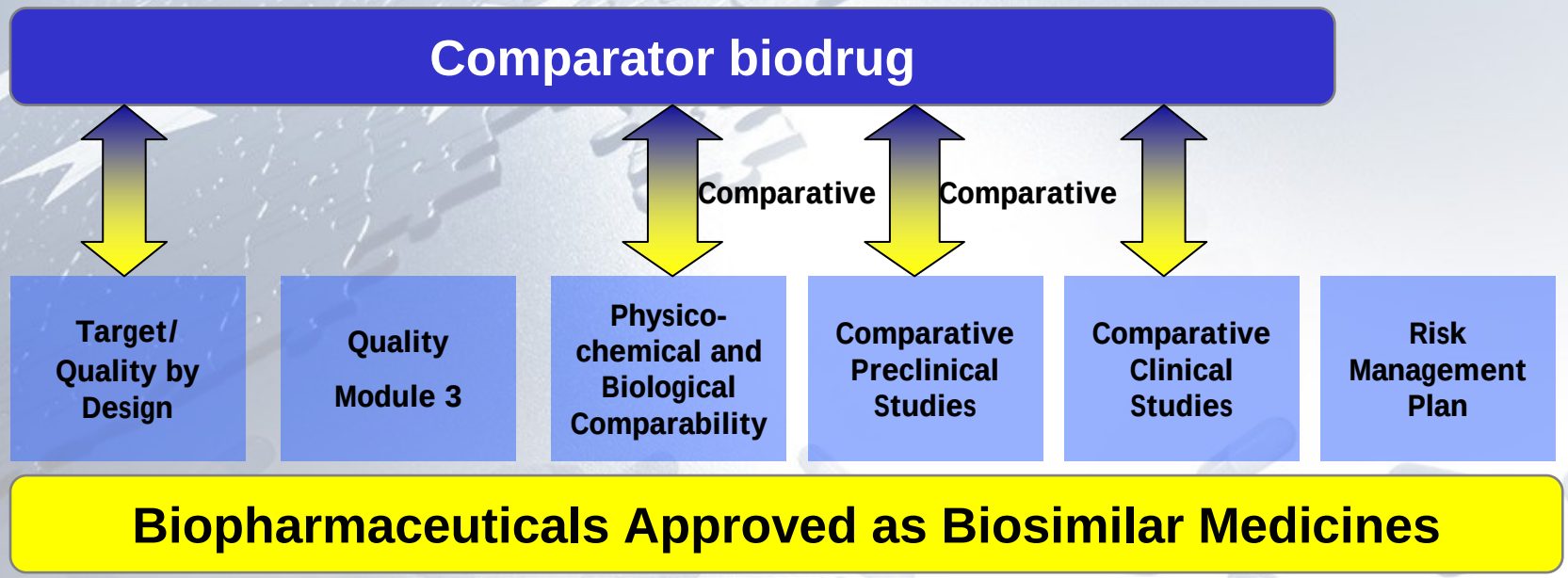
- **Manufacturing process is pro-actively designed to achieve a product equivalent to the comparator biodrug (quality, safety & efficacy)**
  - Extensive characterization of reference product (multiple batches)
  - Broad set of orthogonal state-of-the-art analytical tools
  - Accounting for formulation, 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

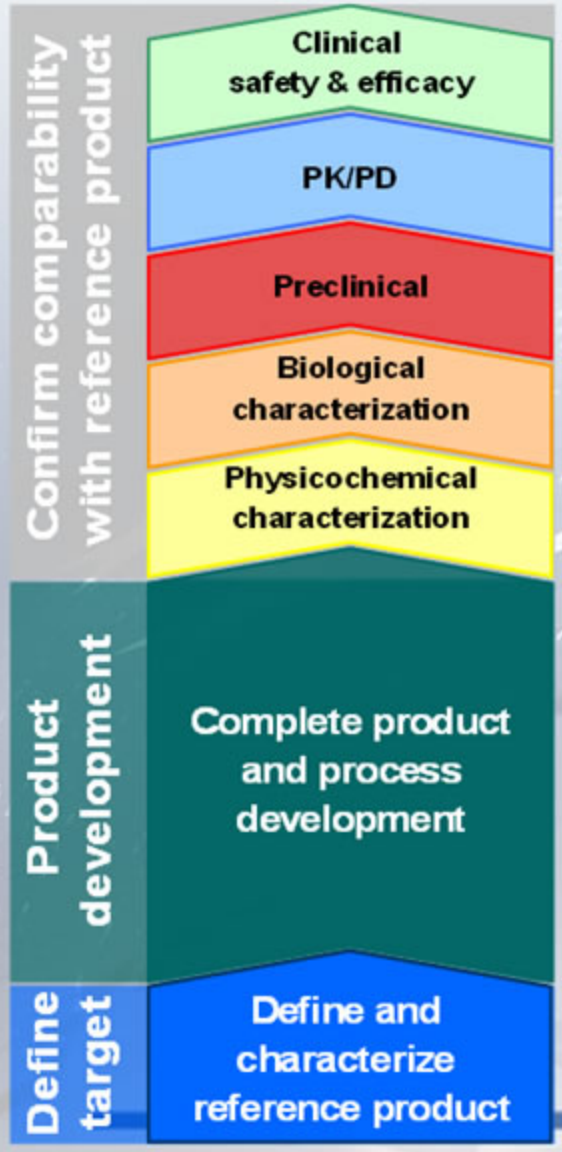
The development of a biosimilar medicine requires a complete product and process development

PLUS

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



The Comparability Exercise – the core element in the Biosimilar Product development



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

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

This rigorous comparability exercise qualifies Biosimilars for **therapeutic interchange**

How close is close enough?

- **The criteria for the comparison of the biosimilar candidate and the comparator biodrug are based on**
  - Understanding batch-to-batch variability of the comparator biodrug
  - 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**

Making Medicines Affordable

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 authorized 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 Follow-on Protein 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

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

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)

Making Medicines Affordable

Status of Biosimilar Products in Europe

EU Biosimilar Approvals

- **Approved substances**
  - Human Growth Hormone
  - Epoetin
  - Filgrastim
- **11 Marketing Authorisations**

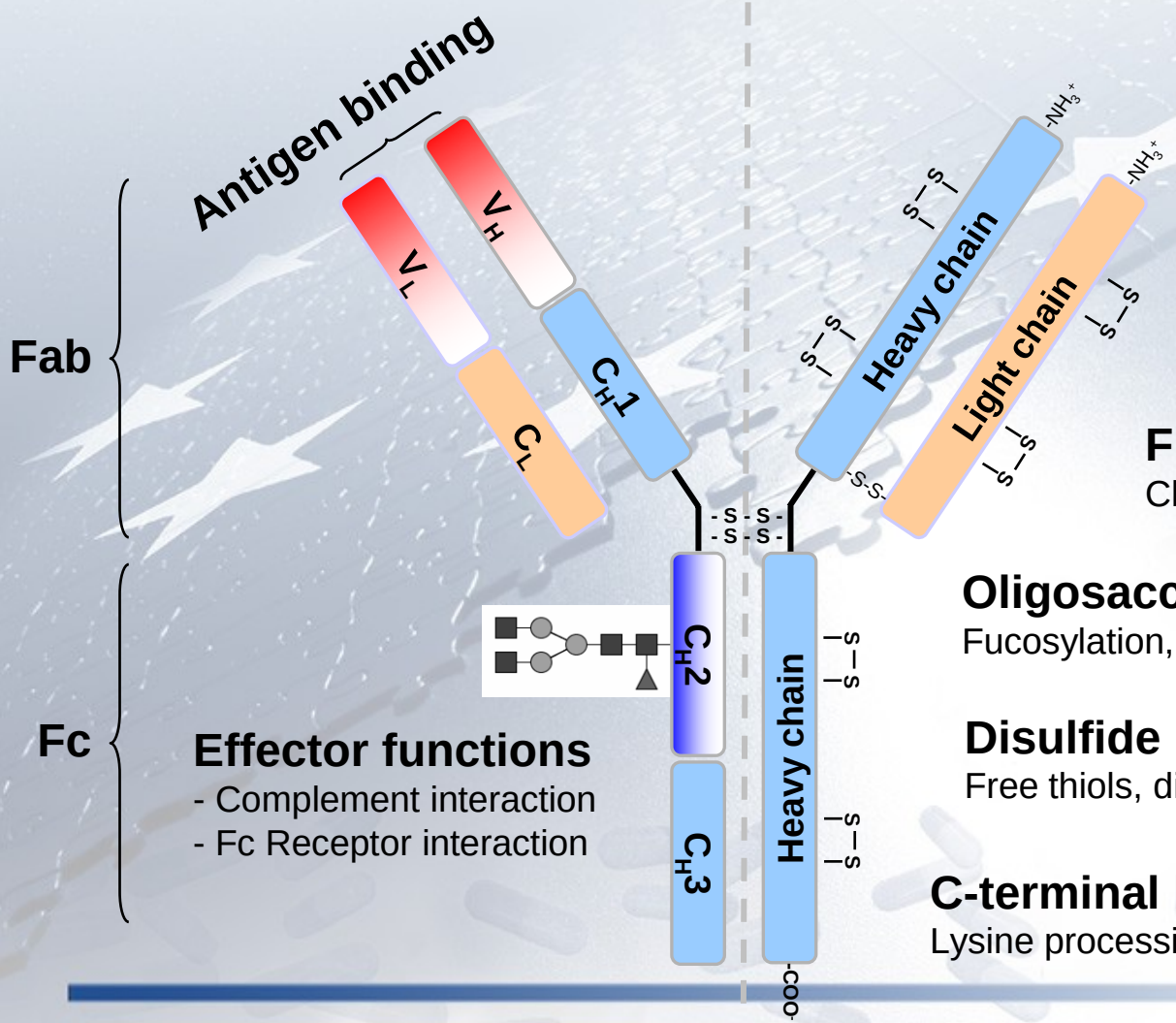
Making Medicines Affordable

The next step
Monoclonal Antibodies

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

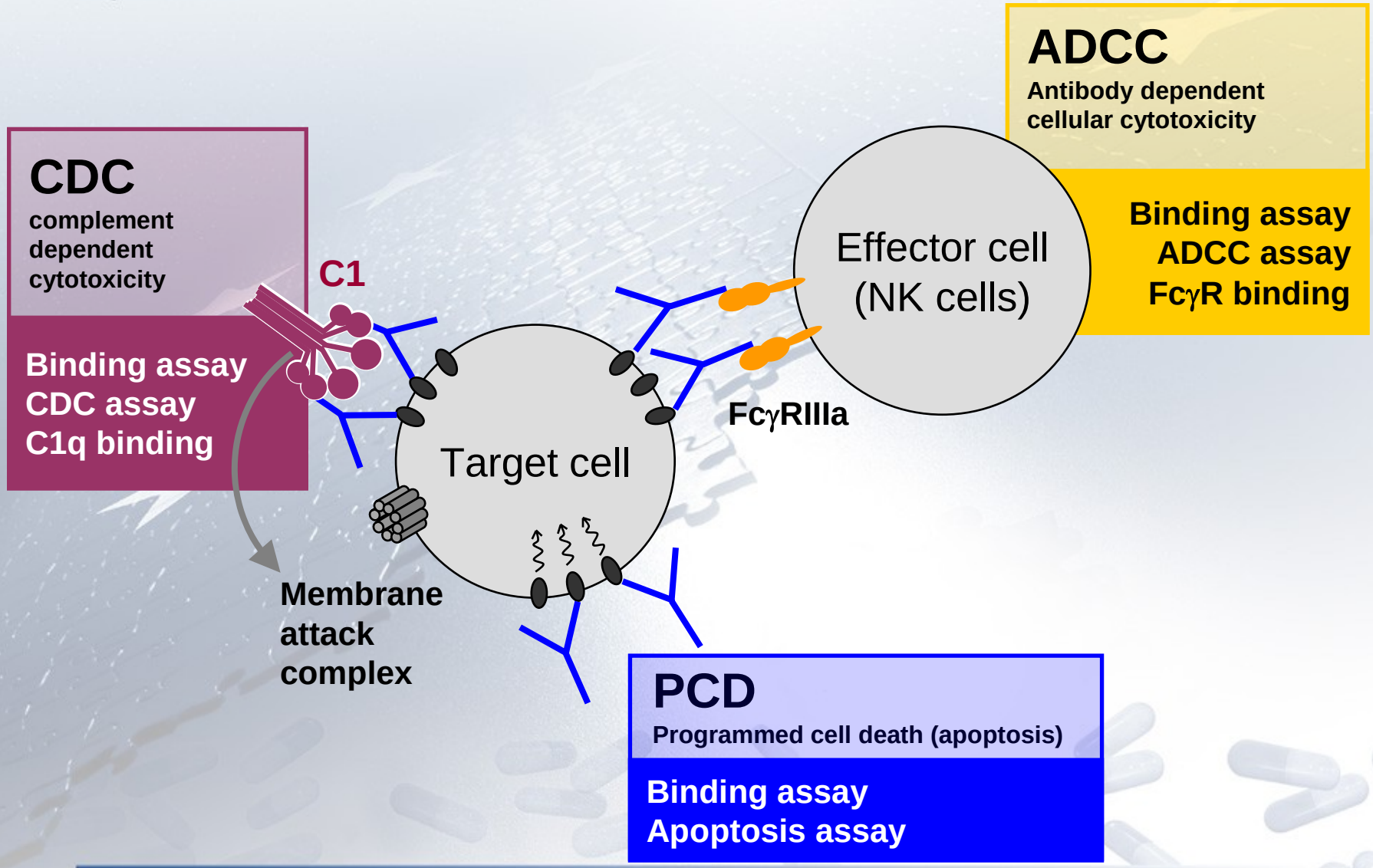
C-terminal heterogeneity
Lysine processing, Proline amidation

Effector functions
- Complement interaction
- Fc Receptor interaction

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: ±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_2L, H, L) and in amino acid chain (p100, p50)	CGE, SDS-PAGE, SEC, RP-HPLC

A toolbox of bioanalytical methods addresses possible mechanisms of action for a mAb



Making Medicines Affordable

Conclusion

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

Making Medicines Affordable

Thank you for your attention

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