Similar biological medicinal product

SSPT, Tunis

13 November 2009

Agence française
de sécurité sanitaire
des produits de santé

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K. HO, Biological department

Similar biological medicinal product
- Biological medicinal product

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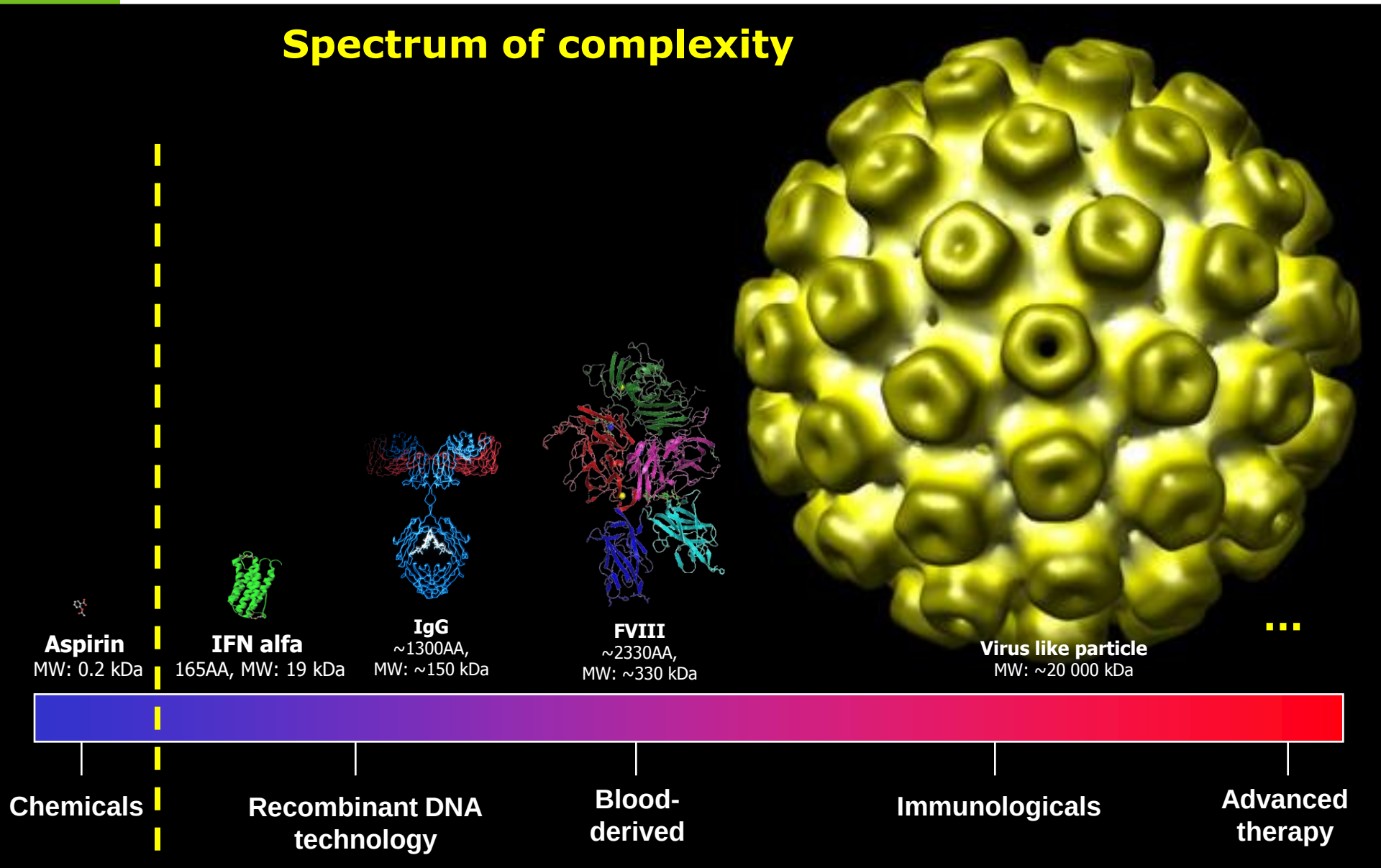
Biological medicinal product
Spectrum of complexity



PHYSICOCHEMICAL CHARACTERISTICS

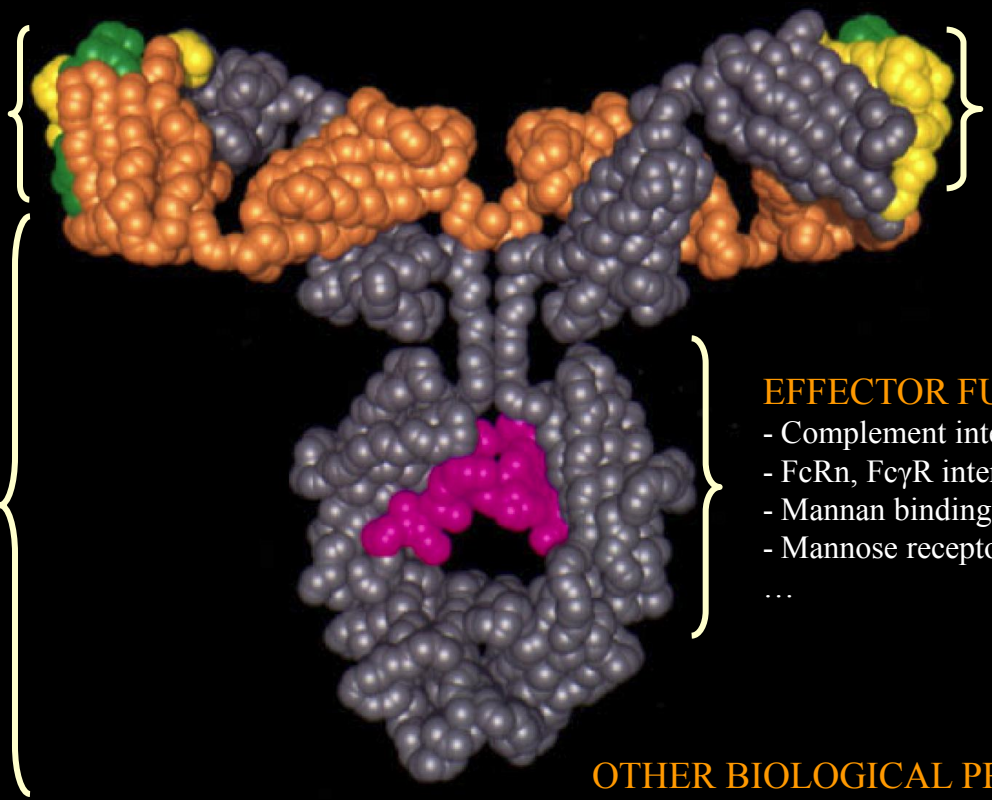
BIOLOGICAL CHARACTERISTICS

VARIABLE REGION
- Deamidation
- Oxidation
- N-term Pyro-Glu
- Glycosylation
- Glycation
- Conformation

…

CONSTANT REGION
- Deamidation
- Oxidation
- Acetylation
- Glycation
- Glycosylation (fucosylation, sialylation, galactosylation, mannosylation…)
- C-term Lys
- Di-sulfide bond shuffling/ cleavage
- Fragmentation/clipping
- Conformation

…



BINDING
- Affinity
- Avidity
- Immunoreactivity / crossreactivity
- Unintentional reactivity

…

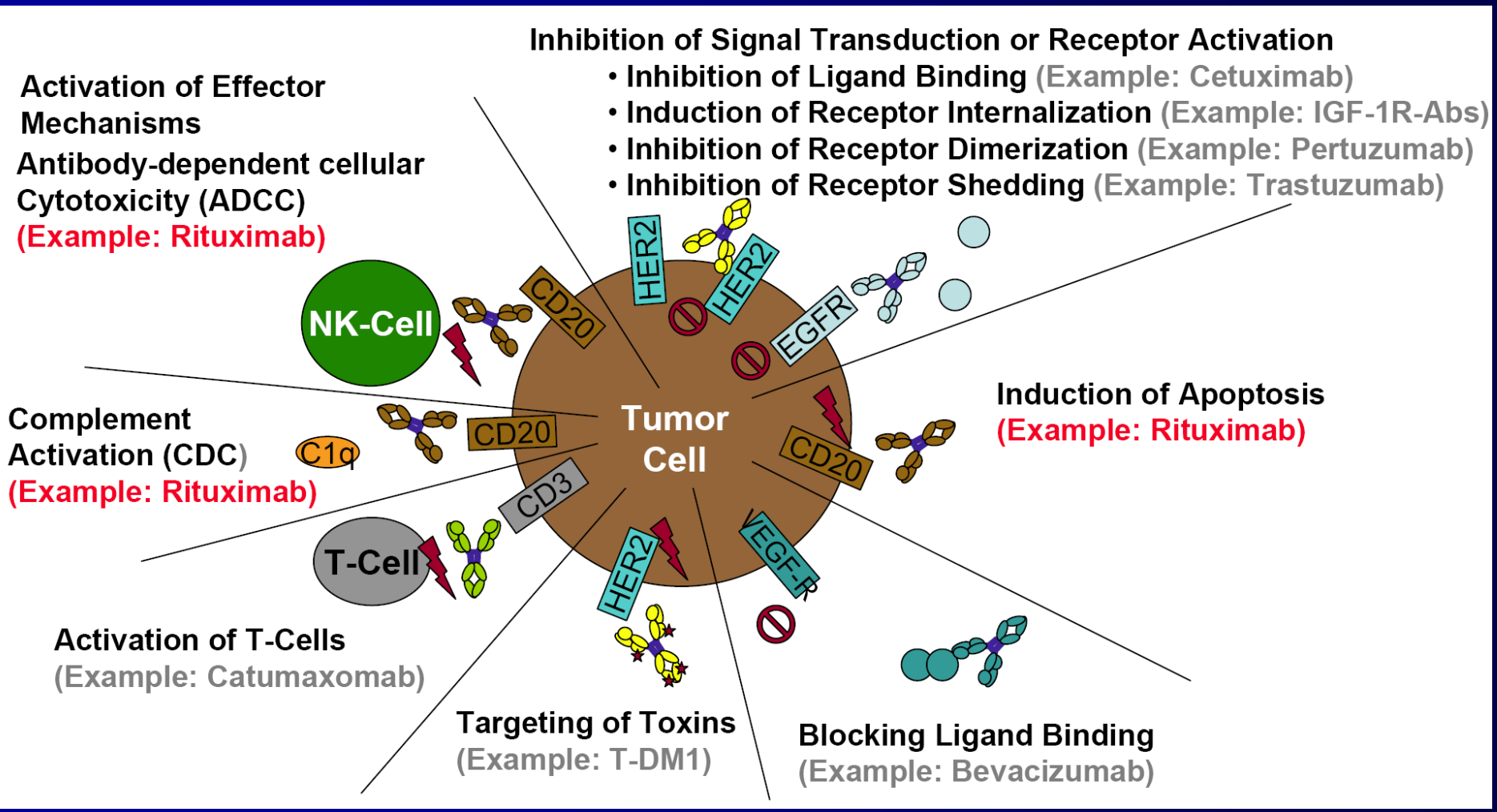
EFFECTOR FUNCTION
- Complement interaction
- FcRn, FcγR interaction
- Mannan binding ligand interaction
- Mannose receptor interaction

…

OTHER BIOLOGICAL PROPERTIES
- PK properties
- Epitope / Immunogenicity
- Modulatory region (Tregitope …)

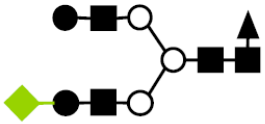
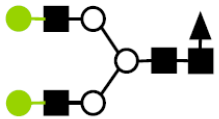
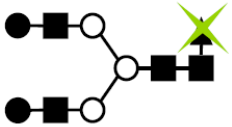
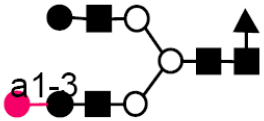
…

Biological medicinal product
Modes of action of Mab



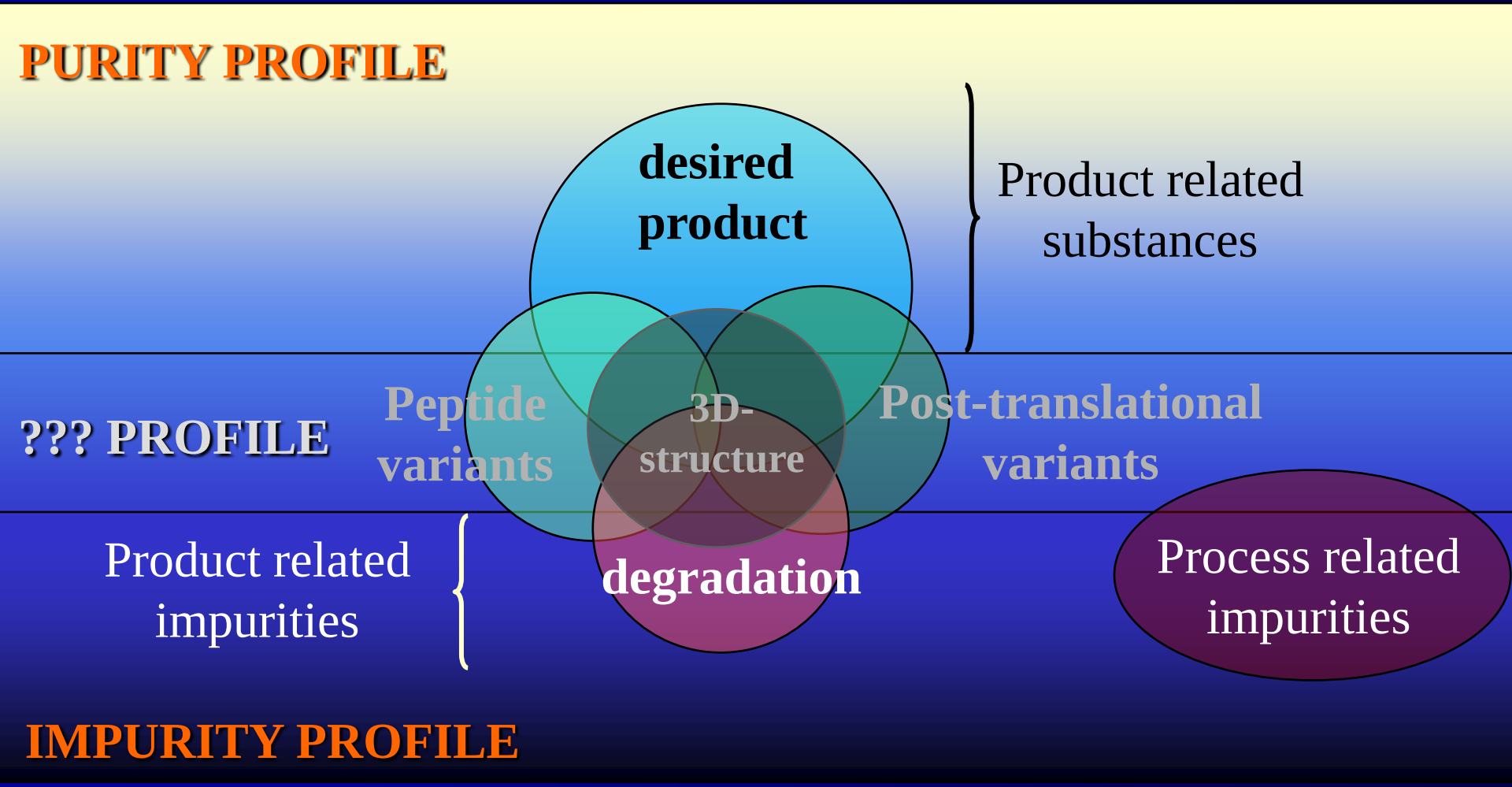
Source: GB Kress, EMEA workshop on biosimilar MAB, 2009

Biological medicinal product
Example: Impact of glycosylation of Mab

GlcNAc/ Mannose		Ligand for Mannose Binding Protein → complement activation (Malhotra *et al.*, Nat. Med. 1995)
Sialic acid		Suppression of ADCC (anti-inflammatory activity) (Kaneko *et al.*, Science 2006)
Galactose		Placental transport (Kibe *et al.*, J. Clin. Biochem. Nutr. 1996)
bisecting GlcNAc		Prevents core fucosylation → enhanced ADCC (Umaña *et al.*, Nat. Biotech. 1999)
absence of core Fucose		Enhanced ADCC (Okazaki *et al.*, J. Mol. Biol. 2004)
α(1-3)-Gal		Non-human/antigenic (Cooper, Xenotransplantation 1998)

Source: GB Kress, EMEA workshop on biosimilar MAB, 2009

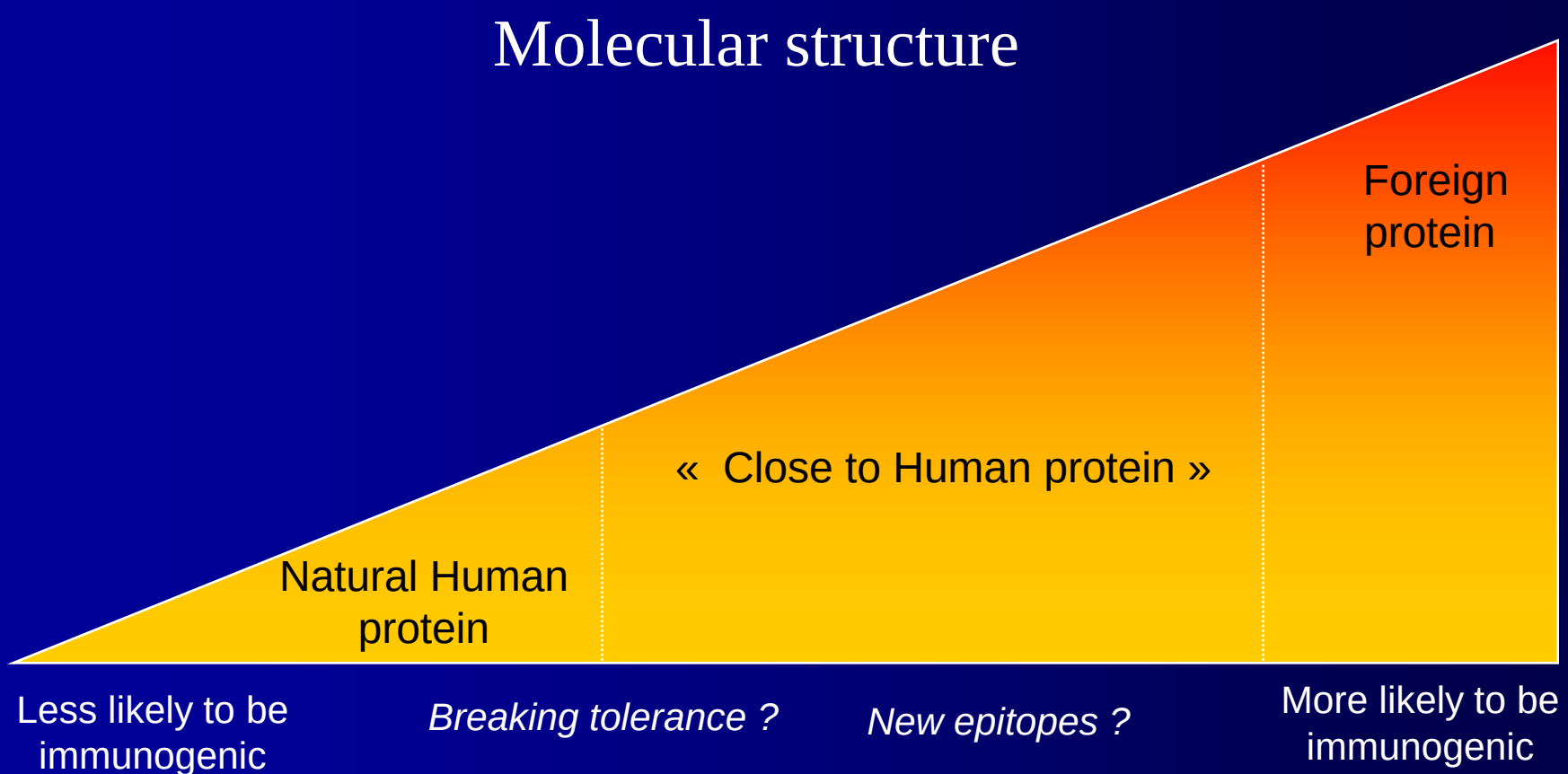
Biological medicinal product
Purity / Impurity profile



Biological medicinal product
Immunogenicity

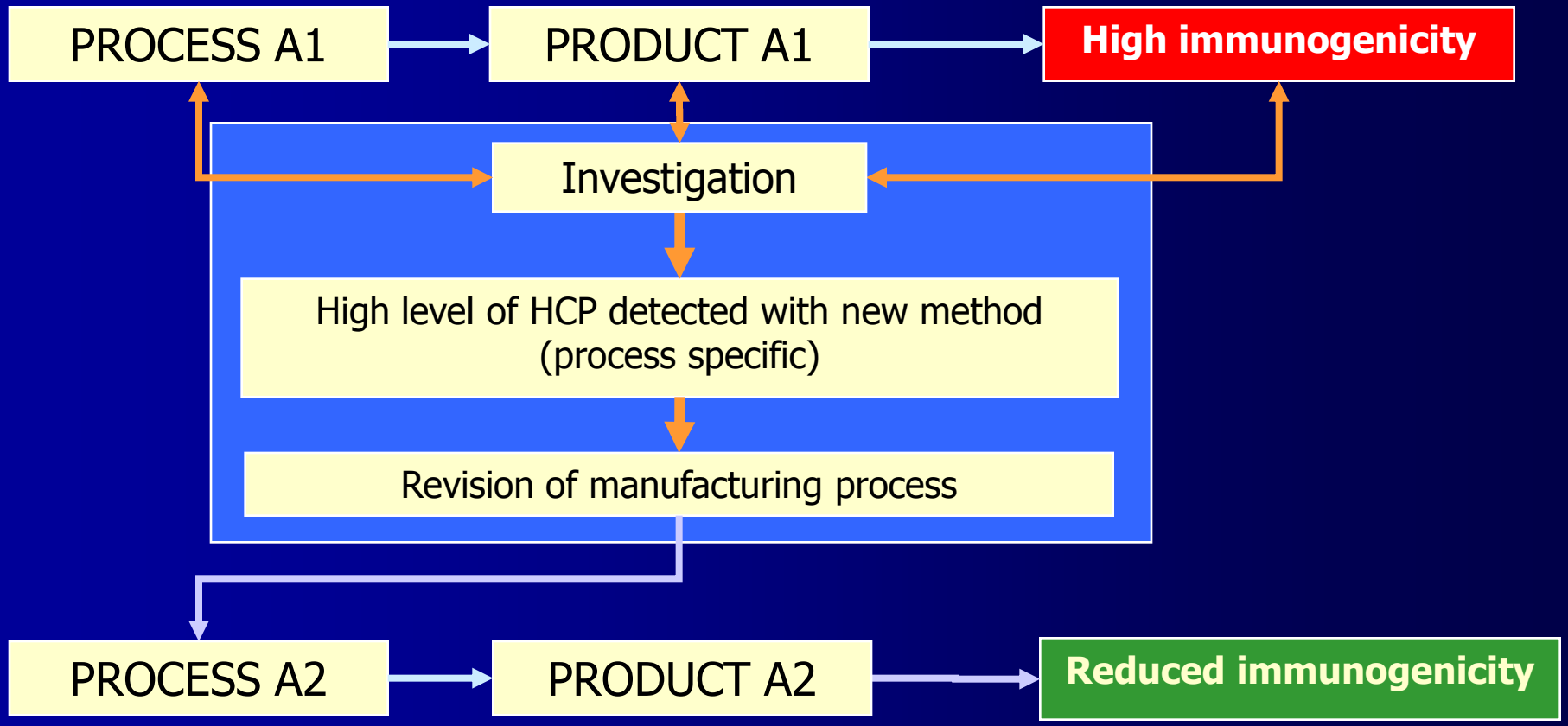
- **The immune system can detect alterations in proteins missed by analytical methods**
  - Immunogenicity of biopharmaceuticals may have serious clinical consequences (e.g. loss of efficacy, cross reaction with endogeneous counterpart, hypersensitivity, anaphylaxis…)
  - Antibodies may be:
    - Non-neutralizing → no impact on clinical efficacy
    - Neutralizing antibodies → inhibition (up to complete loss) of the therapeutic effect

Biological medicinal product
Immunogenicity



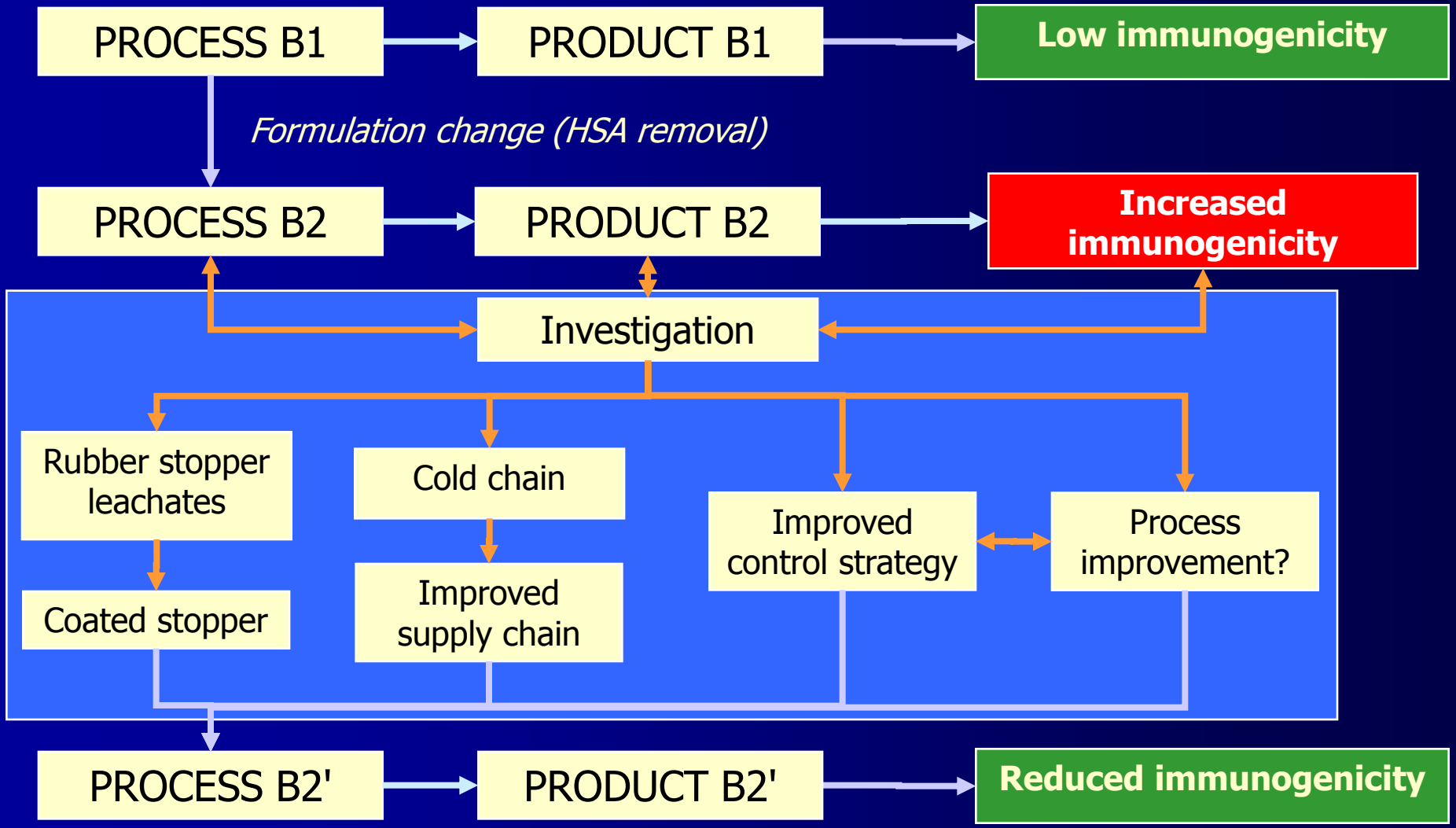
Biological medicinal product

Immunogenicity example – Host Cell Protein (HCP)



Biological medicinal product

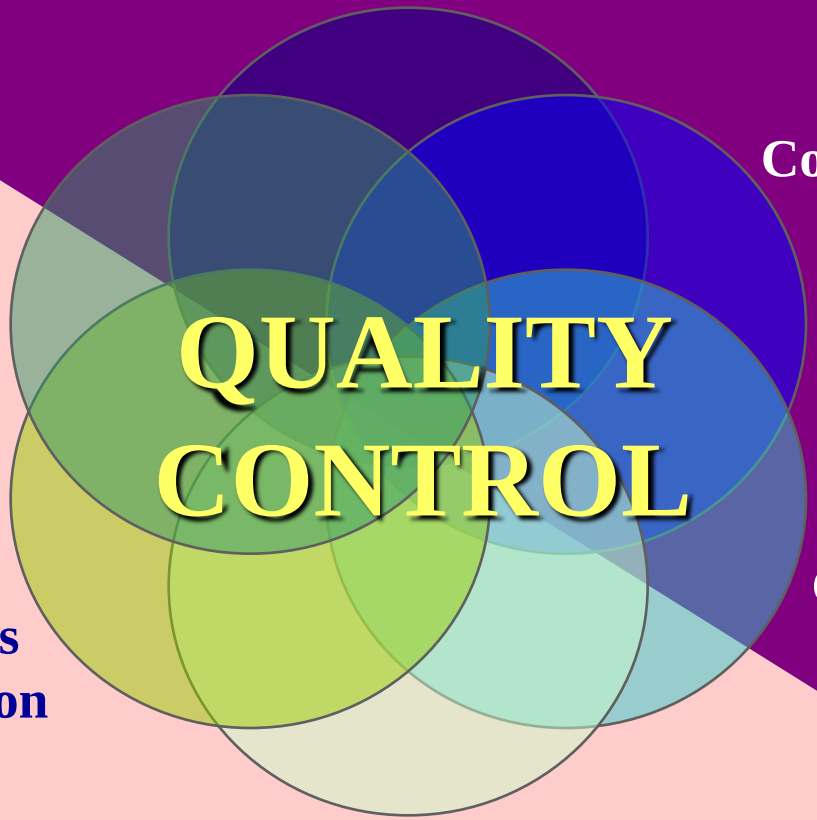
Immunogenicity example – Formulation change



Biological medicinal product
"Biotech paradigm"

- **Analytical challenge:**
  - Complex purity/impurity profile
  - Many unknowns
- **Manufacturing challenge:**
  - One change… a cascade of changes…
  - Necessity to reconsider downstream steps … and upstream steps, as appropriate
  - No *a priori* classification: any change may impact on the quality, safety and efficacy profile
- **Biotechnology derived products are defined by** the product and… its process

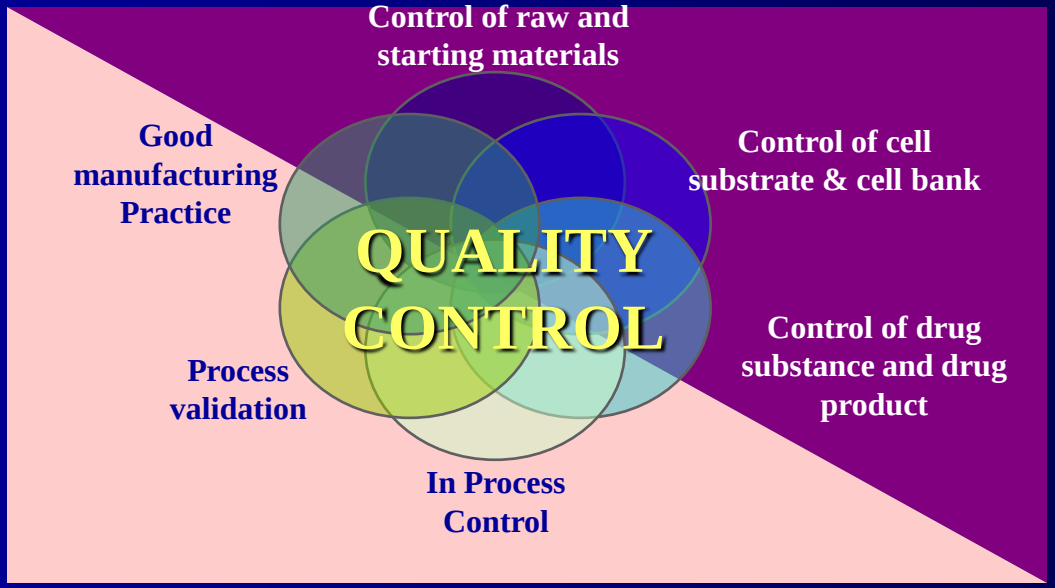
Biological medicinal product
Quality assessment



Biological medicinal product
Quality assessment

Safety & Efficacy profiles

Clinical trial



Similar biological medicinal product
- Biosimilar: EU framework

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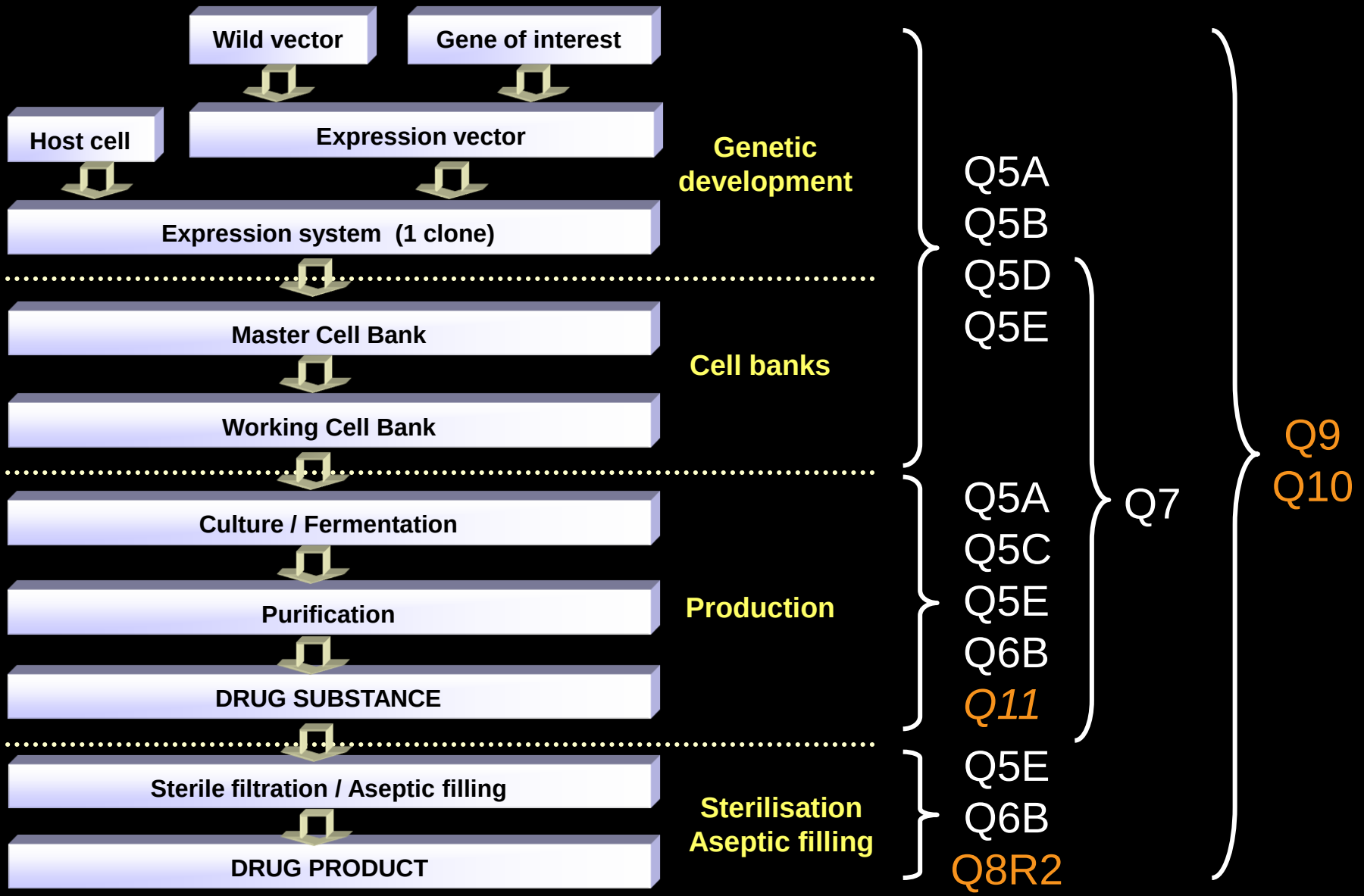
Typical biotech manufacturing process



EudraLex

- Vol 1 : Legislation Human
- Vol 2 : Notice to applicants Human
- Vol 3 : Guidelines Human
- Vol 4 : GMP Human & Veterinary
- Vol 5 : Legislation Veterinary
- Vol 6 : Notice to applicants Veterinary
- Vol 7 : Medicinal products Veterinary
- Vol 8 : MRL Veterinary
- Vol 9 : Pharmacovigilance Human & Veterinary
- Vol 10 : Clinical trials
- EudraLex on CD

5/9/08

The Rules Governing Medicinal Products in the European Union

Introduction

The body of European Union legislation in the pharmaceutical sector is compiled in Volume 1 and Volume 5 of the publication "The rules governing medicinal products in the European Union".

- Volume 1 – EU pharmaceutical legislation for medicinal products for human use
- Volume 5 – EU pharmaceutical legislation for medicinal products for veterinary use

The basic legislation is supported by a series of guidelines that are also published in the following volumes of "The rules governing medicinal products in the European Union":

- Volume 2 - Notice to applicants and regulatory guidelines for medicinal products for human use
- Volume 3 - Scientific guidelines for medicinal products for human use
- Volume 4 – Guidelines for good manufacturing practices for medicinal products for human and veterinary use
- Volume 6 - Notice to applicants and regulatory guidelines for medicinal products for veterinary use
- Volume 7 - Scientific guidelines for medicinal products for veterinary use
- Volume 8 - Maximum residue limits
- Volume 9 – Guidelines for pharmacovigilance for medicinal products for human and veterinary use
- Volume 10 – Guidelines for clinical trial

Medicinal products for paediatric use, orphan, herbal medicinal products and advanced therapies are governed by specific rules.

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm

Background
Quality & Biologicals
Quality (Chemical & Herbal)
Biologicals
Non-Clinical
Clinical Efficacy & Safety
Multidisciplinary

Scientific Guidelines for Human Medicinal Products

Biologicals Guidelines

C = Concept Paper D = Draft Guideline A = Adopted Guideline O = Overview of Comments

Title	C	D	A	O	Reference Number	Publication Date	Effective Date	Other Remarks
Drug Substance								
Manufacture, Characterisation and Control of the Drug Substance								
Production and Quality Control of Monoclonal Antibodies and Related Substances	◆	◆	◆	◆	CHMP/BWP/157653/07	Jan 2009	July 2009	
Potency testing of cell based immunotherapy medicinal products for the treatment of cancer		◆	◆	◆	CHMP/BWP/271475/06	Dec 2007	May 2008	
Quality of biological active substances produced by stable transgene expression in higher plants		◆	◆	◆	CPMP/BWP/48316/06	July 2008	Feb 2009	
Development and Manufacture of Lentiviral Vectors			◆		CPMP/BWP/2458/03	May 2005	Nov 2005	
Production and Quality Control of Animal Immunoglobins and Immunosera for Human Use			◆		CPMP/BWP/3354/99	July 2002	Aug 2002	
Points to consider on the Manufacture and Quality Control of Human Somatic Cell Therapy Medicinal Products			◆		CPMP/BWP/41450/98	May 2001	May 2001	
Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products			◆		CPMP/BWP/3088/99	Apr 2001	Oct 2001	
Development of a CPMP Points to Consider on Xenogeneic Cell Therapy	◆				CPMP/BWP/3326/99	Nov 2000		
Quality of Biotechnological Products: Derivation and Characterisation of Cell			◆		CPMP/ICH/294/95 ICH Topic Q5D	July 1997	Mar 1998	

search ok

Guidelines >>

Q S E M

ICH Japan Symposium 2009 Proceedings available to download

ICH Press Release Yokohama, Japan 6-11 June 2009

Contact the Quality IWG with your comments and questions on Q8, Q9, Q10

General
GCG related
MedDRA related

Quality of Biotechnological Products

Q5A(R1)	*Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*	Q5A
Q5B	*Quality of Biotechnological Products : Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products*	
Q5C	*Quality of Biotechnological Products : Stability Testing of Biotechnological/Biological Products*	
Q5D	*Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products*	
Q5E	*Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process*	

Specifications

Q6A	*Specifications : Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (including Decision Trees)*	
Q6B	*Specifications : Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*	

Good Manufacturing Practice

Q7	*Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*	Q7A

Pharmaceutical Development

Q8(R2)	*Pharmaceutical Development*

Quality Risk Management

Q9	*Quality Risk Management*

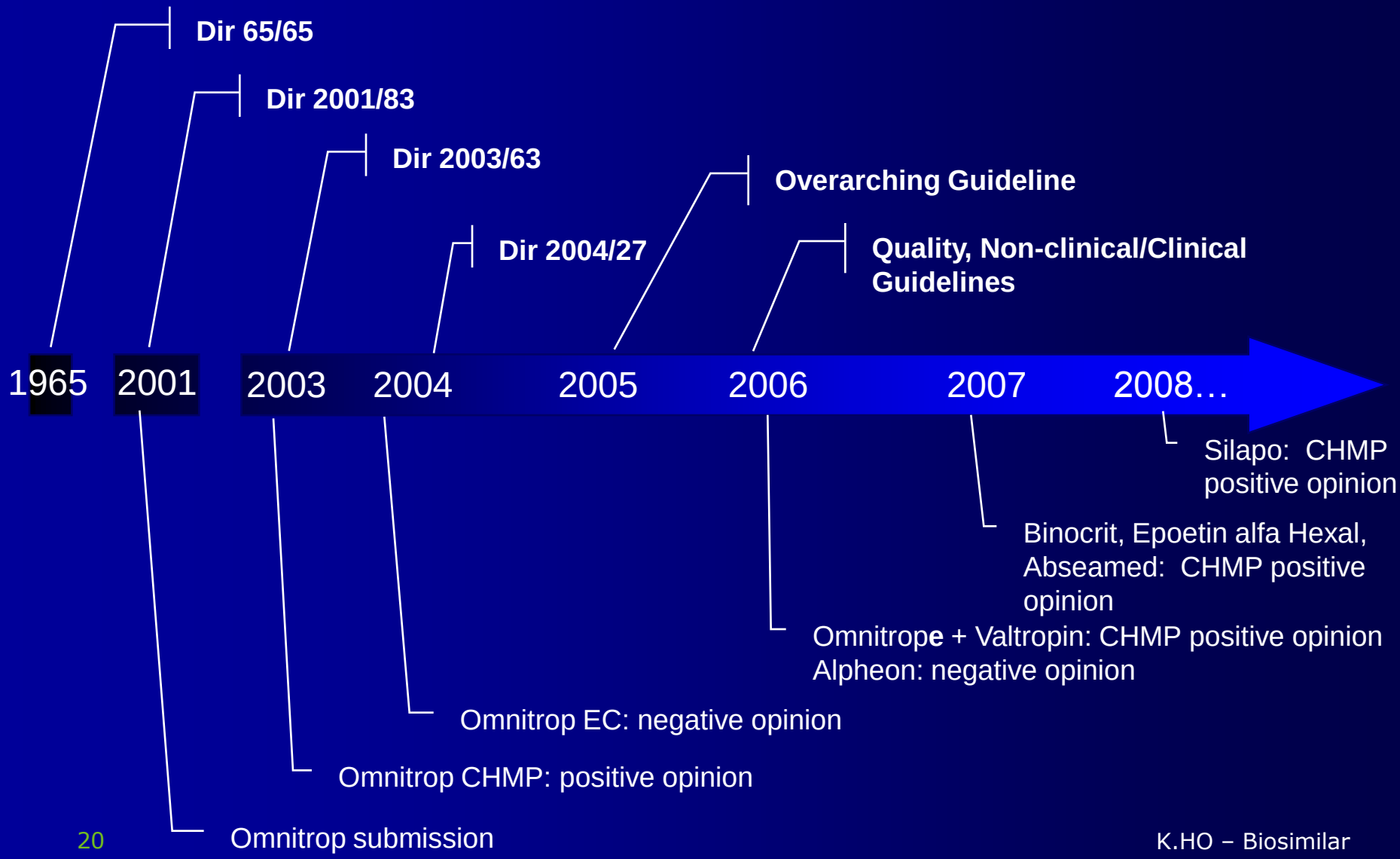
Pharmaceutical Quality System

Q10	*Pharmaceutical Quality System*

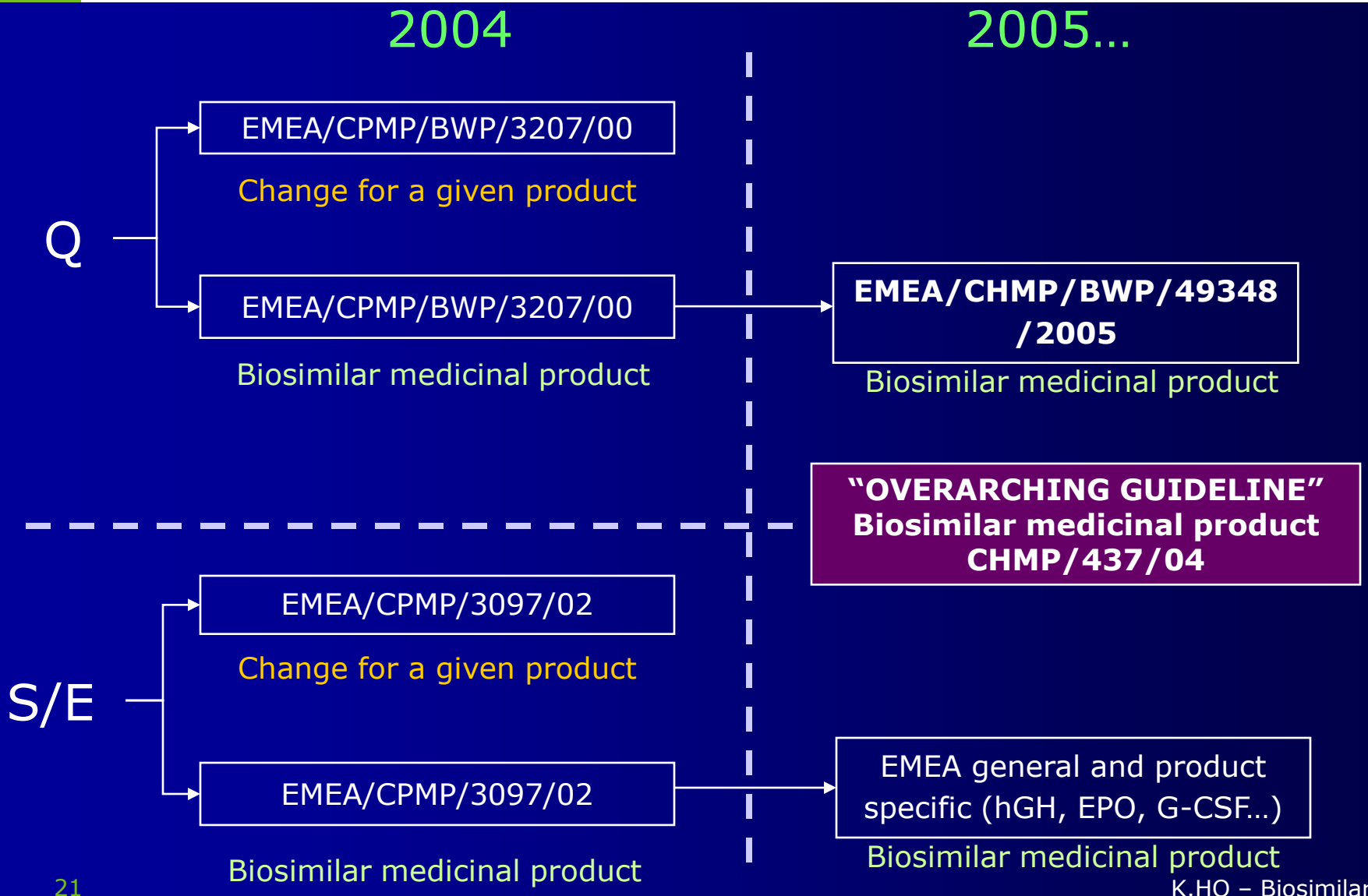
Q8/9/10 Q&As	*Q8/Q9/Q10 - Questions & Answers document*

http://www.ich.org/cache/compo/276-254-1.html

Similar biological medicinal product
Legal environment



Similar biological medicinal product
Comparability guidelines - biosimilar



Similar biological medicinal product
Overview of guidelines

User guide -
Draft 2004 / Adopted 2005

Overarching Guideline (CHMP/437/04).
"Guideline on Similar Biological Medicinal Products"
Defines key concepts / principles (information reference)

Biotechnology- derived proteins

Quality Issues
Draft 2005 / Adopted 2006

(Non)clinical
Draft 2005 / Adopted 2006

Class specific

Quality

Non-clinical

Clinical

ADOPTED	REVISION	FUTURE
- Insulin (2006) - Somatropin (2006) - Epoetin (2006) - GCSF (2006) - IFNα (2009) - LMWH (2009)	- Epoetin (ongoing)	- Novel/ different expression systems - Monoclonal antibody ? …

Similar biological medicinal product
« Overarching guideline »

- **Guideline on similar biological medicinal products (CHMP/437/04)**
  - Scope: Any biological medicinal product
    - Biotechnology derived protein
    - Immunogicals (e.g. vaccines and allergens): unlikely, but case by case…
    - Blood products or recombinant alternatives: reduced clinical dossier not acceptable
    - Others (e.g. gene, cell therapy): considered in the future in the light of scientific knowledge and regulatory experience gained at the time…
  - "Generic approach": not appropriate to biologics due to complexity of molecular structure and/or production
  - Biosimilarity to be established at all levels: Q / S / E
  - Importance to clearly identify the product to support pharmacovigilance monitoring
  - When pharmaceutical form or strength or route of administration are not the same: must be supported by non-clinical/clinical trials
  - Reference medicinal product: must be authorised in the Community on the basis of a complete dossier

Similar biological medicinal product
Quality guideline

- **Quality guideline (CHMP/BWP/49348/2005)**
  - Scope:
    - recombinant DNA-derived proteins.
    - Principles apply to proteins and peptides, their derivatives and products of which they are components (e.g. conjugates).
  - Manufacturing process:
    - Own development + state of the art information
    - Own process related impurities
    - Suitability of the proposed formulation to be demonstrated, even if same as reference product.
    - Generate clinical data for the comparability study with product manufactured with the final manufacturing process (i.e. representing quality profile of the batches to be commercialised)

Similar biological medicinal product
Quality guideline

- **Quality guideline (CHMP/BWP/49348/2005)**
  - Comparability exercise versus reference product
    - Comparison against official data (e.g. pharmacopoeial monographs or against other published scientific data): not sufficient
    - Quality attributes:
      - not expected to be identical.
      - Limits: not wider than the range of variability of the reference product
      - Differences: to be justified in relation to safety and efficacy.
    - Reference product:
      - Comparability for medicinal product + active substance
      - Same reference for all three parts of the dossier (Q/S/E)
      - To be clearly identified (brand name, pharmaceutical form, formulation and strength …)
      - Shelf life of the reference product to be considered

Similar biological medicinal product
Non-clinical / Clinical

- **Non-clinical / Clinical (CHMP/BMWP/42832/2005)**
  - Indication(s):
    - Each claimed indication: should be justified or demonstrated separately
    - Extrapolation: possible but depends on clinical experience, available literature data, same mechanisms of action or receptor(s) involved in all indications
  - Non-clinical studies
    - Comparative in nature; designed to detect differences
    - Pharmacodynamic + At least 1 repeat dose toxicity study
    - Safety pharmacology, reproduction, mutagenicity and carcinogenicity: usually not required

Similar biological medicinal product
Non-clinical / Clinical

- **Non-clinical / Clinical (CHMP/BMWP/42832/2005)**
  - Clinical studies
    - Generate clinical data with the final manufacturing process…
    - Pharmacokinetics (PK) + Pharmacodynamics (PD) studies
      - Comparative PK/PD studies may suffice to demonstrate clinical comparability, in some situations
    - Efficacy trials
      - Confirmatory comparative trial(s), normally in line with ICH E10
      - If comparative design not feasible: to be discussed with competent authorities

Similar biological medicinal product
Non-clinical / Clinical

- **Non-clinical / Clinical (CHMP/BMWP/42832/2005)**
  - Clinical Safety and pharmacovigilance
    - Even if comparable: may have different safety profile
    - Pre-authorisation clinical studies: insufficient to identify all potential differences: safety closely monitored post-approval.
      - Risk specification to be provided
      - Risk management programme / Pharmacovigilance plan to be provided
  - Immunogenicity
    - 1 year follow-up data usually required pre-licensing

Similar biological medicinal product
- Conclusion

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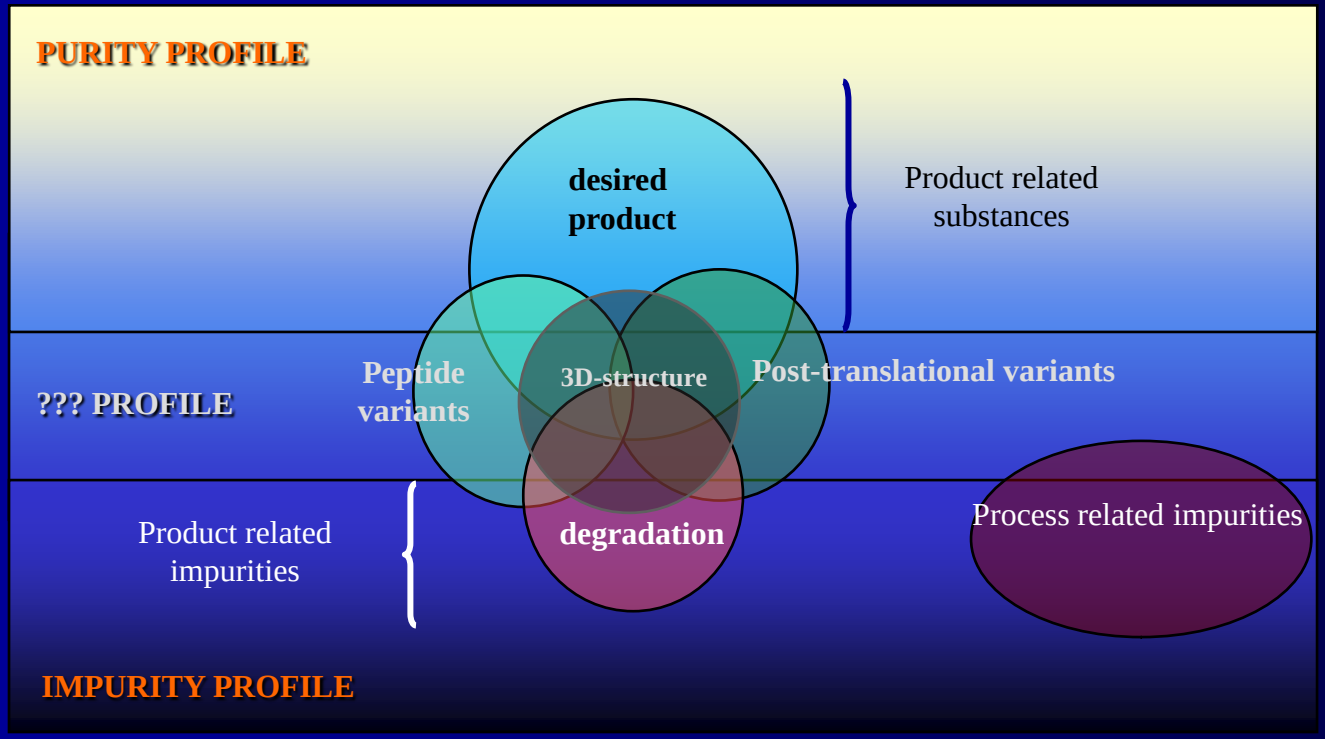
Similar biological medicinal product
Conclusion

- **Biotech product:**
  - complex structure
  - Immunogenicity issues +++



Similar biological medicinal product
Conclusion

- **Similar biological medicinal product**
  - Legal framework introduced in Dir 2001/83 as amended
  - Applicant may choose to file as:
    - Stand-alone application (i.e. full dossier), or
    - Biosimilar approach: reduction of non-clinical and clinical data compared to a full dossier

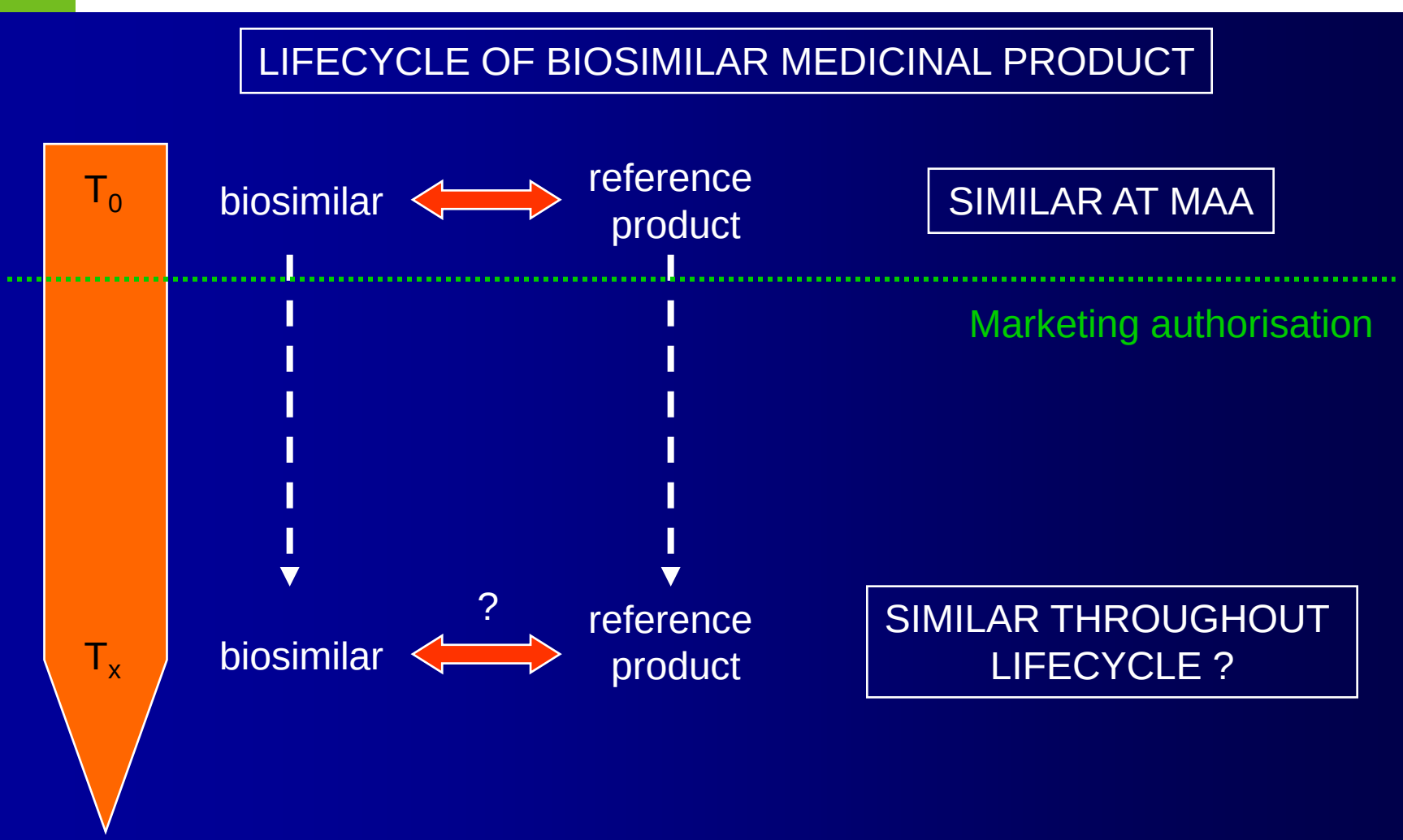
- **Comparability exercise:**
  - Similar ≠ identical
  - Studies principally comparative Q + S + E
  - Reference product must be authorized in the EU
  - Same reference product for all aspects of the comparability exercise
  - Pivotal studies: final process material

Similar biological medicinal product
Biosimilar MAA (status June 2009)

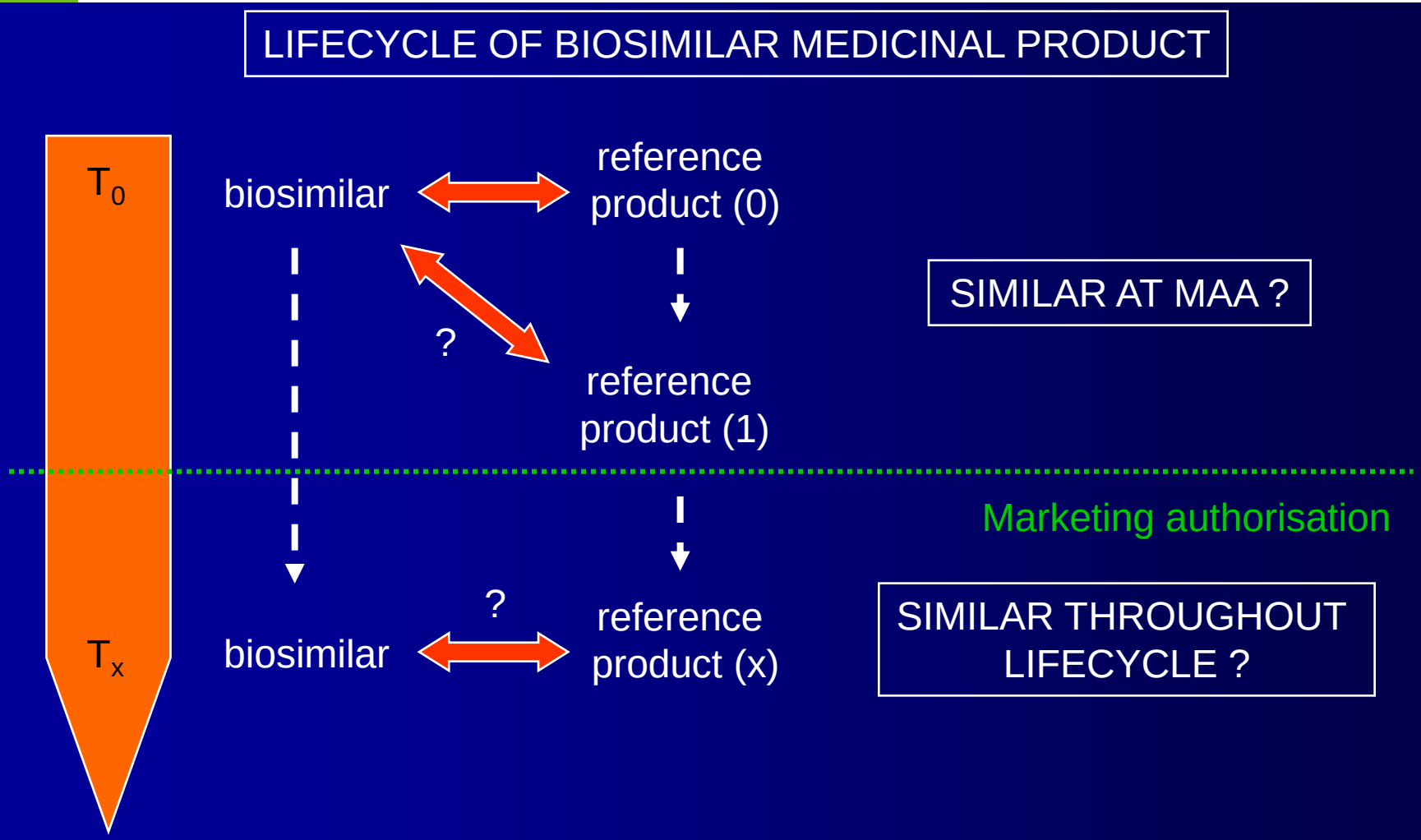
1	Omnitrope (somatropin)	Sandoz	Authorised
2	Valtropin (somatropin)	Biopartners	Authorised
3	Alpheon (interferon alfa)	Biopartners	Negative
4	Binocrit (epoetin alfa)	Sandoz	Authorised
5	Epoetin alfa Hexal (epoetin alfa)	Hexal	Authorised
6	Abseamed (epoetin alfa)	Medice	Authorised
7	Silapo (epoetin zeta)	Stada	Authorised
8	Retacrit (epoetin zeta)	Hospira	Authorised
9	Insulin Marvel Short (human insulin)	Marvel Life Sci'	Withdrawn
10	Insulin Marvel Intermediate (human insulin)	Marvel Life Sci'	Withdrawn
11	Insulin Marvel Long (human insulin)	Marvel Life Sci'	Withdrawn
12	Filgrastim Ratiopharm (filgrastim)	Ratiopharm	Authorised
13	Ratiograstim (filgrastim)	Ratiopharm	Authorised
14	Biograstim (filgrastim)	CT Arzneimittel	Authorised
15	Tevagrastim (filgrastim)	Teva	Authorised
16	Filgrastim Hexal (filgrastim)	Hexal	Authorised
17	Zarzio (filgrastim)	Sandoz	Authorised

Source: X. Luria, EMEA workshop on biosimilar MAB, 2009

Similar biological medicinal product
Conclusion



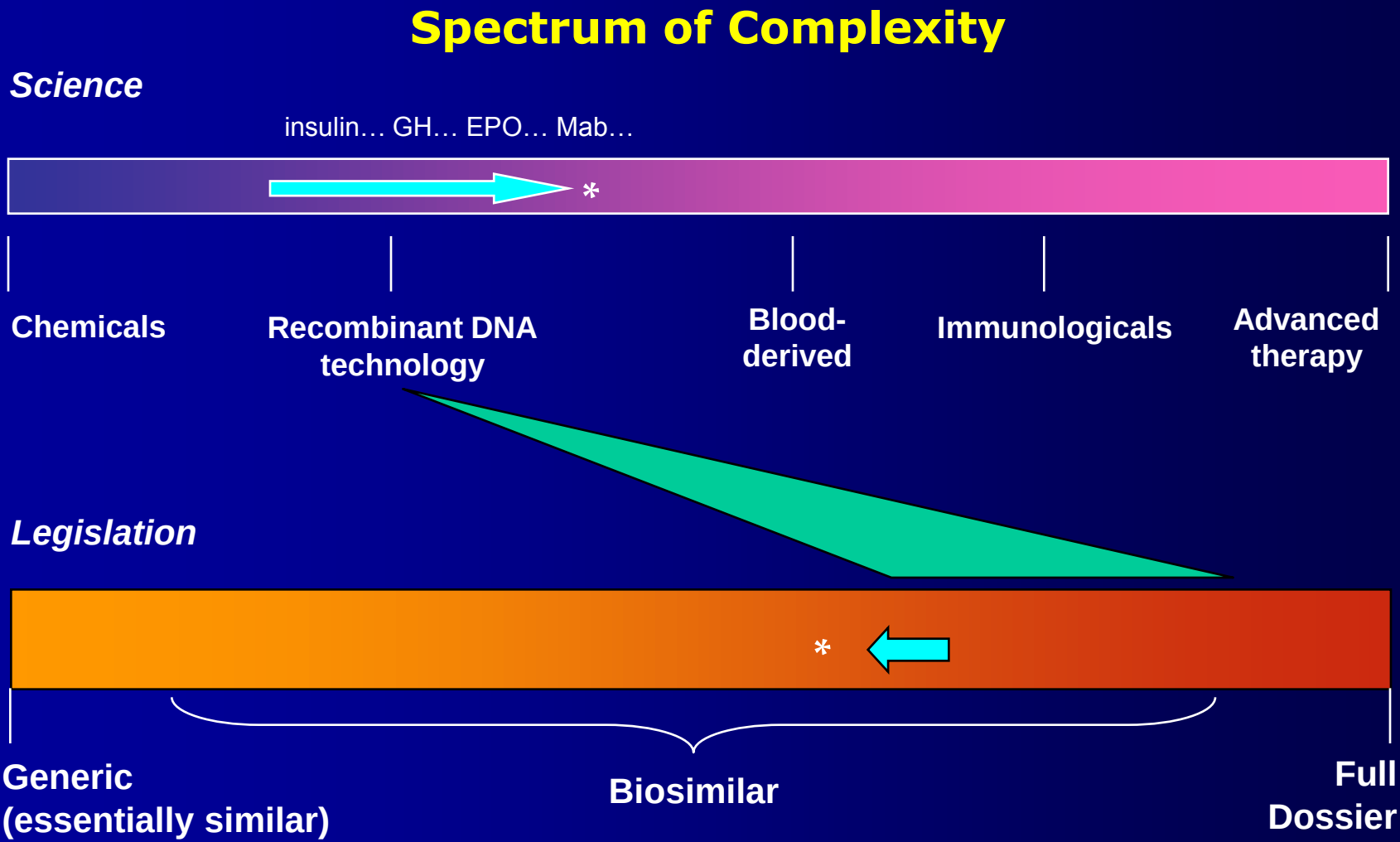
Similar biological medicinal product
Conclusion



Similar biological medicinal product
Conclusion

- **Interchangeability / Substitution**
  - Beyond the scope of the current guidelines: National issues…
  - Not exclusive problem of biosimilars (e.g. Somatropin)
  - INN: ongoing challenge...
  - "Biosimilars" are not "generics"; they are BIOlogical medicinal products that are SIMILAR to another one already marketed.
    - BIOlogical products: not recommended to switch patients from a biological product to another without therapeutic justification
    - SIMILAR biological products:
      - No reason to deviate from general recommendations for biologics
      - A systematic and uncontrolled substitution, based on prescription on INN of the active substance does not appear reasonable at this time
  - Recommendation:
    - NO "AUTOMATIC" SUBSTITUTION
    - SWITCH: UNDER SUPERVISION BY HEALTHCARE PROFESSIONAL

Similar biological medicinal product
Perspective



Adapted from: J. Purves, BMWP/BWP training 2007