ICH
harmonisation for better health

Quality of biologicals

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Biotechnology derived product

- **Macromolecule not chemically synthesisable or extractable in sufficient quantity: ex. erythropoietin (EPO)**
  - 165 AA glycoprotein produced by kidney
  - Trace level in urines
  - Kidney failure: insufficient production of endogenous EPO ⇨ Anaemia

- **Therapeutic alternative / Viral safety: ex. somatropin (GH):**
  - 191 AA protein produced by pituitary gland
  - Initially extracted from human cadaver ⇨ Creutzfeld-Jakob disease

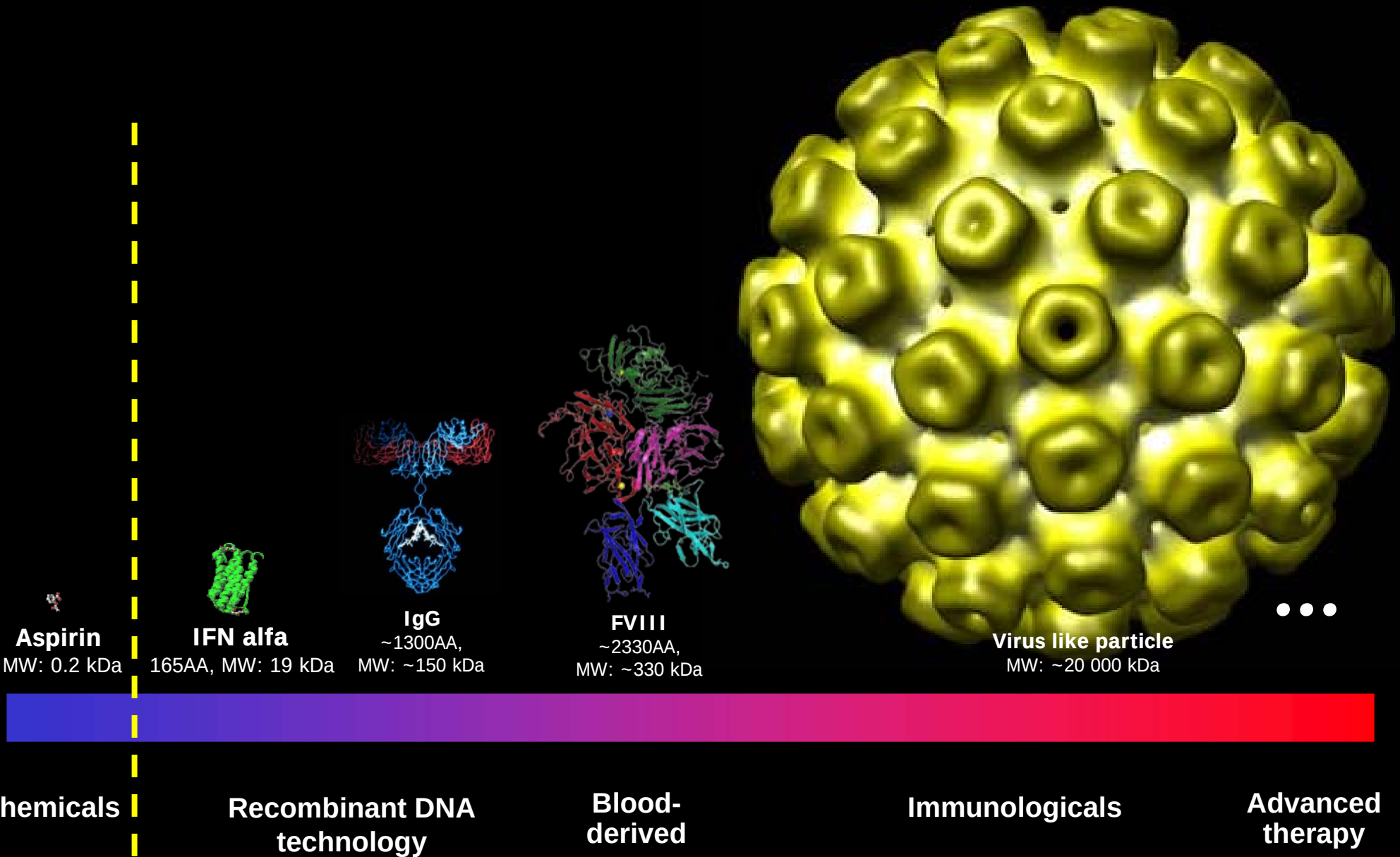
- **Non-existing protein: ex. humanised immunoglobulin**
  - Creation de novo
  - Murine variable region + Human constant region

Biotechnology derived product

- **Blood derived factors (tPA,activated protein C, FVIIa, FVIII, FIX…)**
- **Cytokines & growth factors (EPO, IFN α, IFN-β1, PEG-IFN-α, IL-1, G-CSF, PDGF…)**
- **Hormones (insulin, somatropin, FSH, hCG, LH, TSH, calcitonin, PTH…)**
- **Vaccine (Anti-hepatitis B…)**
- **Enzymes (β-glucocerebrosidase, α-galactosidase…)**
- **Monoclonal antibodies**
  - Immunosuppressor, Crohn disease
  - Breast cancer, non-Hodgkin lymphoma, LLC
  - Coronary failure
  - VRS infection
  - Asthma et allergy
  - Diagnostic

  …

Spectrum of complexity



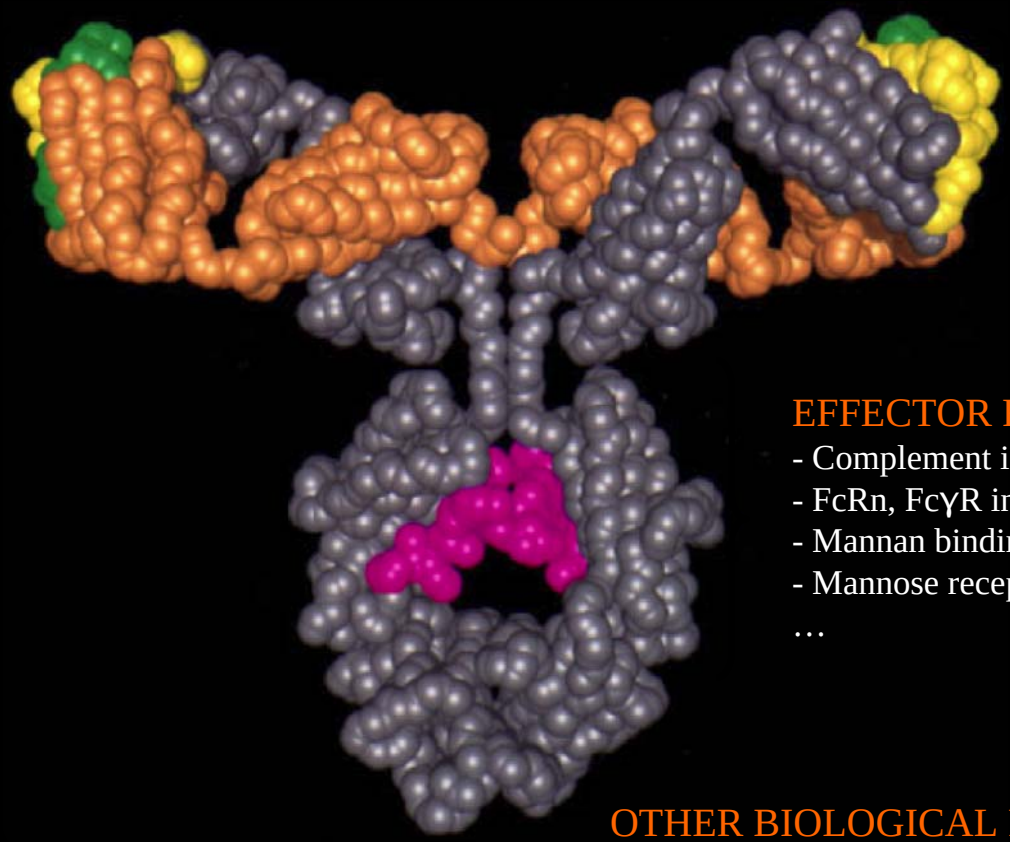
PHYSICOCHEMICAL CHARACTERISTICS

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

…



BIOLOGICAL CHARACTERISTICS

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

…

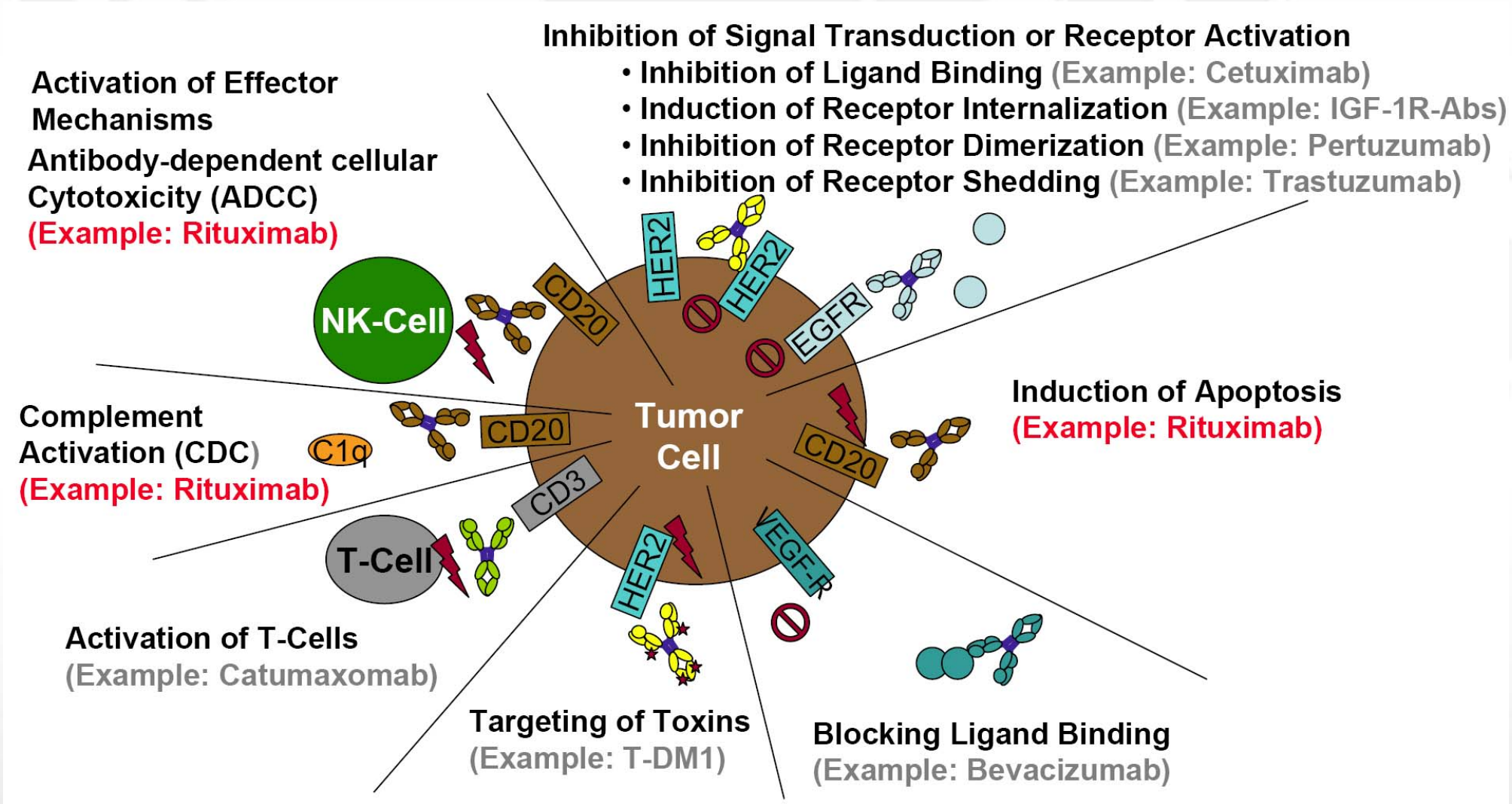
EFFECTOR FUNCTION
- Complement interaction
- FcRn, FcγR interaction
- Mannan binding ligand interaction
- Mannose receptor interaction

…

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

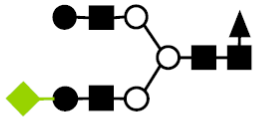
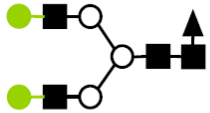
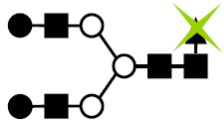
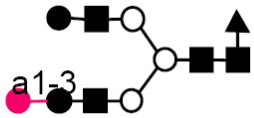
…

Modes of action of Mab



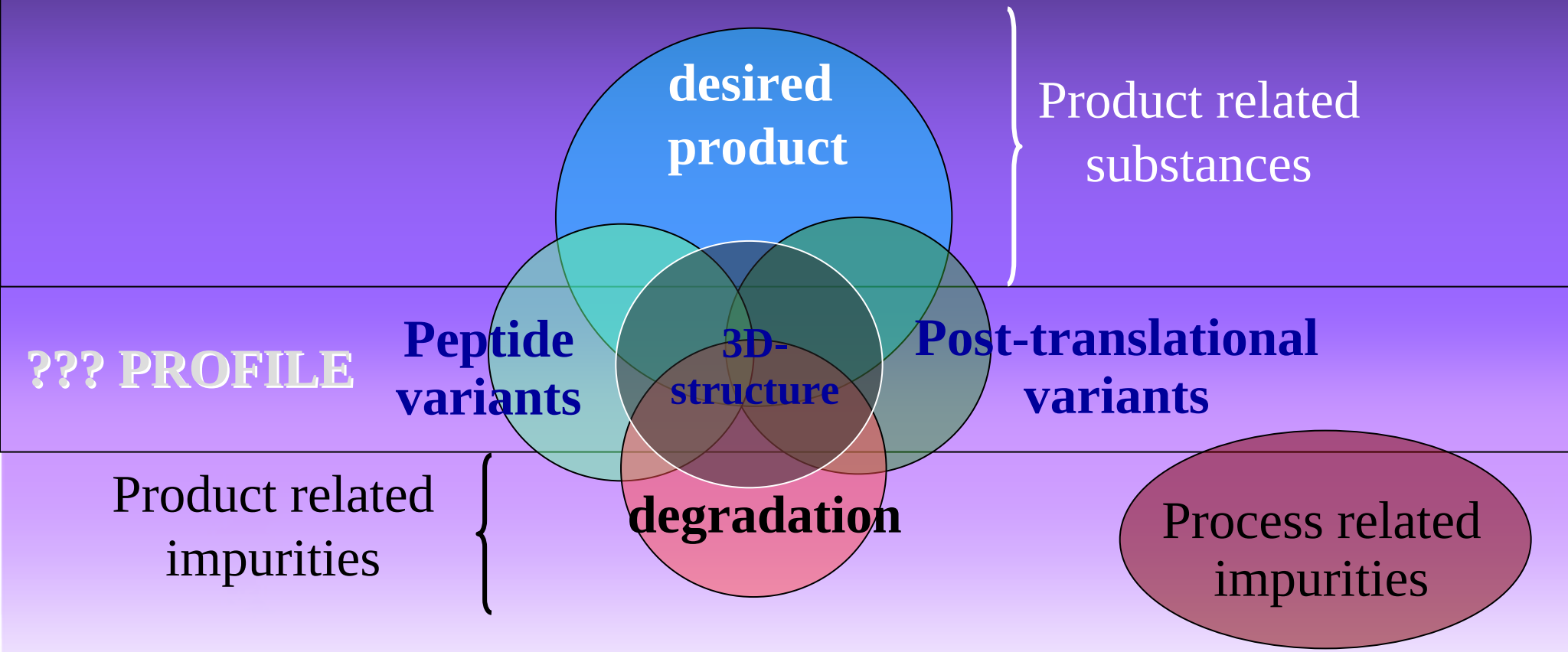
Source: GB Kress, EMEA workshop on biosimilar MAB, 2009

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)

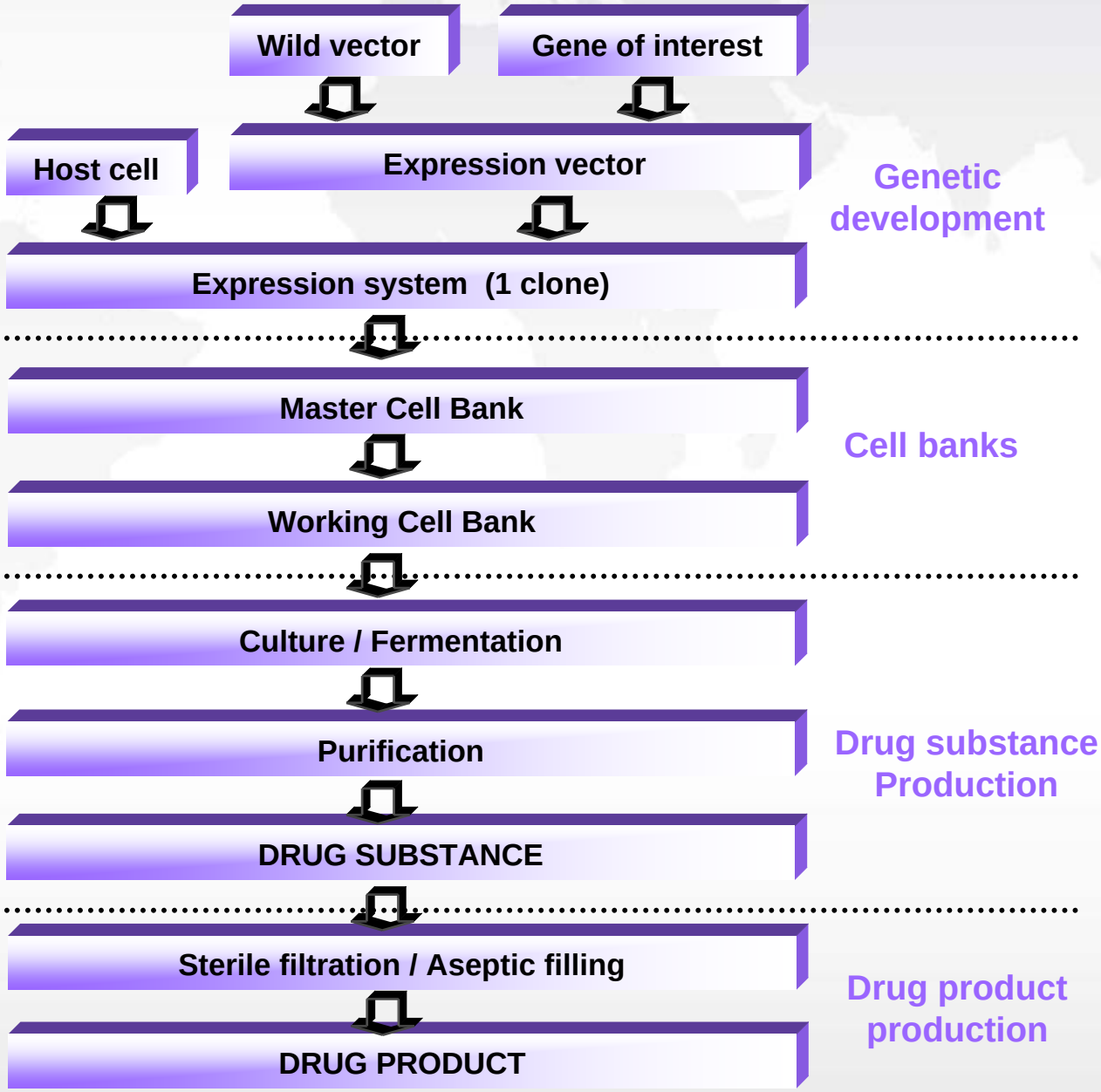
Source: GB Kress, EMEA workshop on biosimilar MAB, 2009

PURITY PROFILE

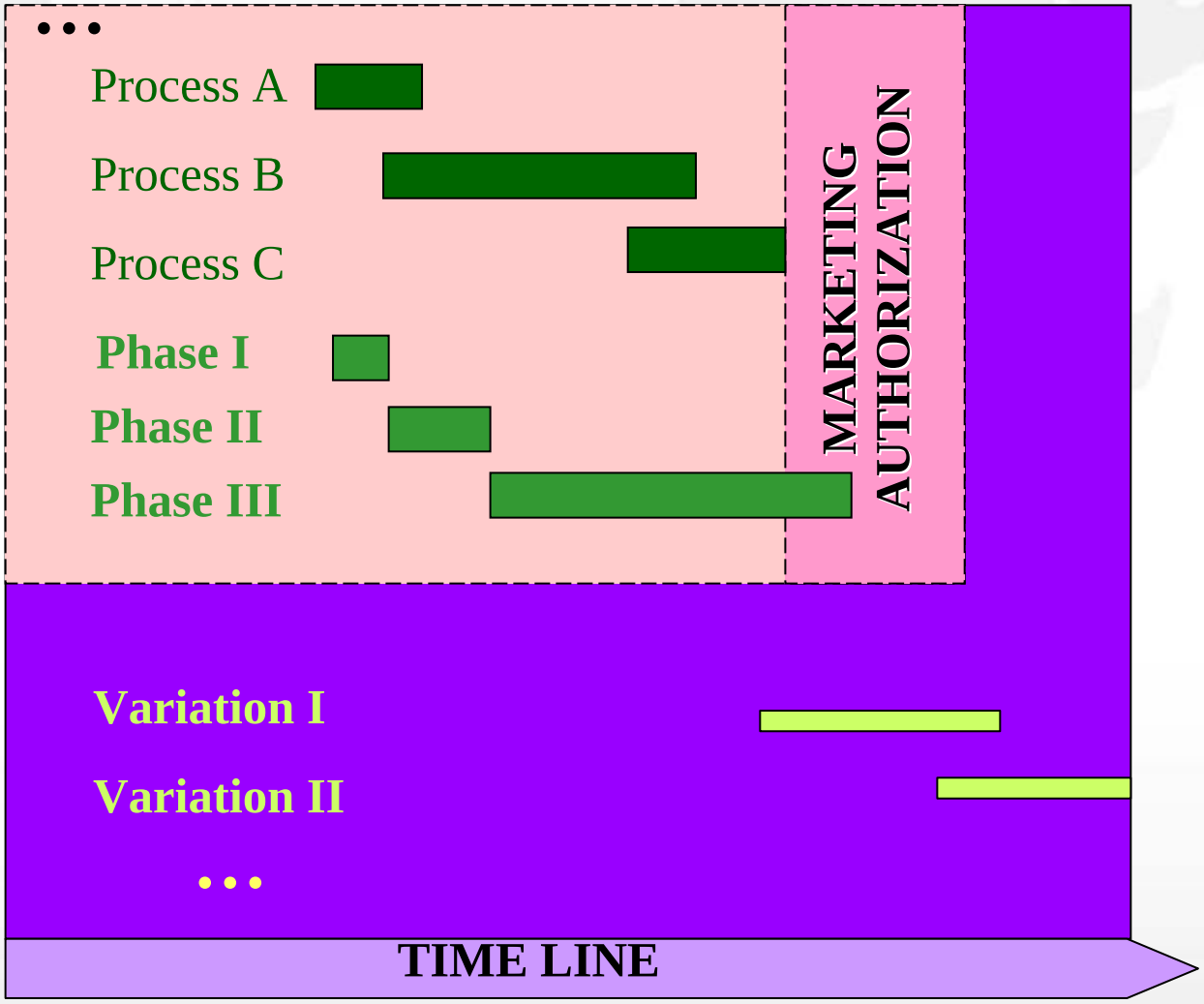


IMPURITY PROFILE

Typical biotech manufacturing process



Product life cycle



Life cycle of a given product:

⇨ Continuous research & development

⇨ Improvement of Quantity /Quality (productivity, viral safety aspects, presentations…)

Example of process change

- Expression system
- Fermentation/culture process
- Purification process
- DRUG SUBSTANCE

- Formulation and filling
- DRUG PRODUCT

Change from FCS

to gamma-irradiated FCS

⇩

Change in cell growth properties

⇩

Increase of protein load at recovery

⇩

Adaptation Purification process

Example of process change

- Expression system
- Fermentation/culture process
- Purification process
- DRUG SUBSTANCE

- Formulation and filling
- DRUG PRODUCT

Need to adapt the expression system

⇧ retrospectively

Serum free process

⇩

Change in cell growth

and productivity

⇩

Adaptation Purification process

Example of process change

- Expression system
- Fermentation/culture process
- Purification process
- DRUG SUBSTANCE

- Formulation and filling
- DRUG PRODUCT

Change in Purification and Harvest

⇩

General improvement of purity profile,

increase of aggregate,

change in isomer distribution

Example of process change

- Expression system
- Fermentation/culture process
- Purification process
- DRUG SUBSTANCE

- Formulation and filling
- DRUG PRODUCT

Change in buffer

⇩

Desorption of process impurities from filters

Example of process change

- Expression system
- Fermentation/culture process
- Purification process
- DRUG SUBSTANCE

- Formulation and filling
- DRUG PRODUCT

Change in filling volume

(same container closure system)

⇩

Adaptation of freeze drying procedure

⇩

Change in stability properties

Example of process change

- Expression system
- Fermentation/culture process
- Purification process
- DRUG SUBSTANCE

- Formulation and filling
- DRUG PRODUCT

Change in speed of

introduction of excipient

⇩

Change in particle distribution consistency

⇩

EFFICACY/SAFETY PROFILE

Example of process change

- Expression system
- Fermentation/culture process
- Purification process
- DRUG SUBSTANCE

- Formulation and filling
- DRUG PRODUCT

Hold-time increase of

formulated bulk prior filling

⇩

Increased evaporation

⇩

OVERDOSE

Example of process change

- Expression system
- Fermentation/culture process
- Purification process
- DRUG SUBSTANCE

- Formulation and filling
- DRUG PRODUCT

Change in filling tip

⇩

Increase in aggregates

Example of process change

- Expression system
- Fermentation/culture process
- Purification process
- DRUG SUBSTANCE

- Formulation and filling
- DRUG PRODUCT

Removal of HSA

⇩

Adaptation of formulation

⇩

IMMUNOGENICITY PROFILE

IN PATIENTS

Example of process change

- Expression system
- Fermentation/culture process
- Purification process
- DRUG SUBSTANCE

- Formulation and filling
- DRUG PRODUCT

Change in cleaning of filters

⇩

Leachables

⇩

VISIBLE PARTICULATES

Quality profile

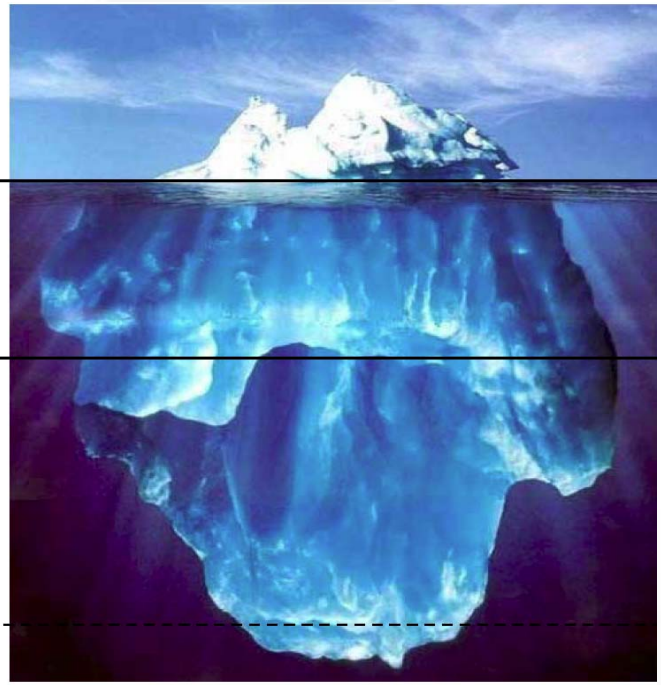
Release Tests (Specifications)

Extended Characterization
(Process & Product)

Process Control

- Procedures
- Materials
- In-process testing
- Monitoring
- Validation

Unknown
Learned over time – update control strategy



from: Koszlowski, S. & Swann, P. (2006) Adv. Drug Delivery Revs.


Control of raw and starting materials
Product
Control of process parameters
Control of intermediates
QUALITY
Control of drug substance and drug product
Process validation & evaluation
Process
Good manufacturing Practice

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.

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	

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Welcome to ICH

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry of Europe, Japan and the US to discuss scientific and technical aspects of drug registration. Since its inception in 1990, ICH has evolved, through its ICH Global Cooperation Group, to respond to the increasingly global face of drug development, so that the benefits of international harmonisation for better global health can be realised worldwide. ICH's mission is to achieve greater harmonisation to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. Download the ICH 20th Anniversary Publication

Discover ICH Products

Safety Guidelines

ICH has produced a comprehensive set of safety guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy ... (more)

View All Safety Guidelines

ICH Training

SADC training workshop on the ICH Q7 Guideline
End of June 2011, Arusha, Tanzania

ICH Quality Q8/Q9/Q10 training follow up in Japan
25 April 2011, Tokyo, Japan.

ASEAN workshop on the ICH Q5C Guideline
30-31 May 2011, Kuala Lumpur, Malaysia

GCC training workshop on ICH Q5A to Q5E Guidelines
19-20 April 2011, Riyadh, Saudi Arabia

Help to Shape the ICH Guidelines

by responding to one of our consultations. Your contribution will then be considered by the relevant ICH Working Group.

Draft Guidelines
Q&A Documents

Recent News

14 March 2011

Quality IWG training material on Q8/Q9/Q10

To extend the benefits of the three ICH regional workshops on the ICH Q8/Q9/Q10...

28 February 2011

Follow in details the main decisions taken by the ICH governing body in November 2010

A comprehensive report of the last meeting of the ICH Steering...

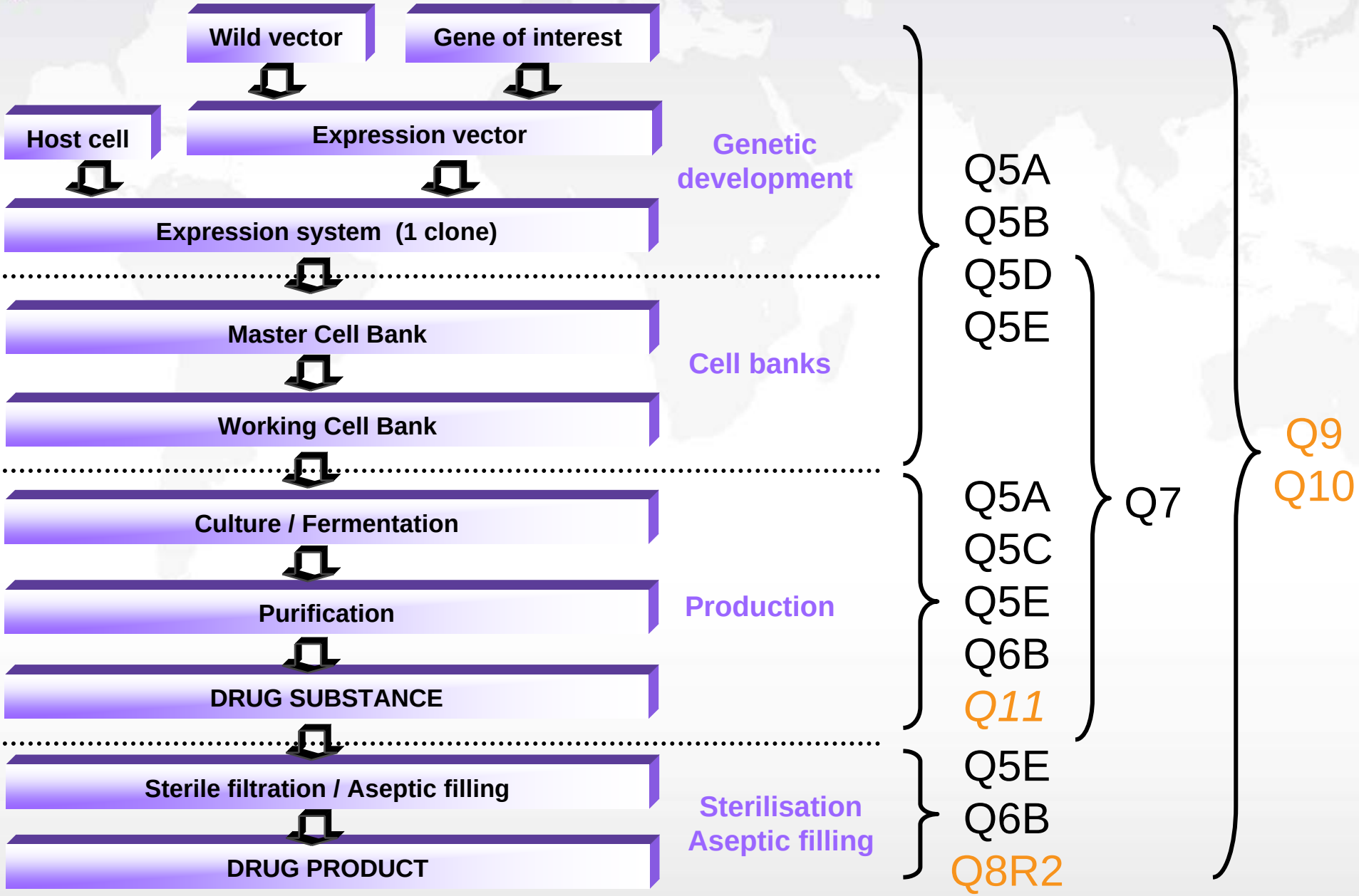
17 February 2011

Revised PDE for Cumene: ICH Q3C(R5)

The ICH Expert Working Group (EWG) responsible for the maintenance of the Q3C...

http://www.ich.org

Typical biotech manufacturing process



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Thank You!

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