European Experience with Similar Medicinal Biological Products

5th Japanese Biologics forum (JBF)

National Institute of Health Sciences (NIHS)

Tokyo, 16th January, 2008

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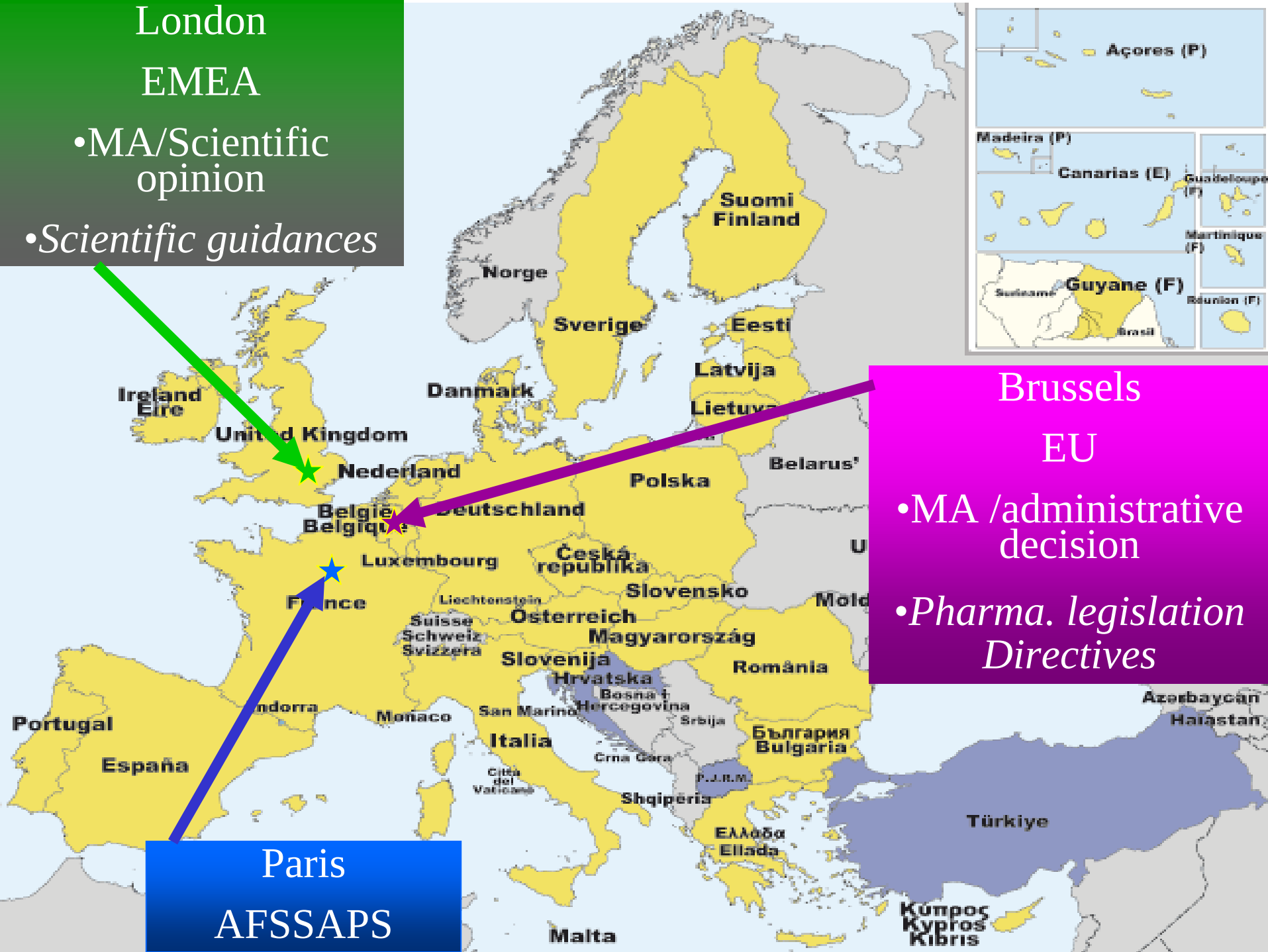
de sécurité sanitaire
des produits de santé

afssaps

P.ZORZI

Department for Evaluation of Biologics


London
EMEA
•MA/Scientific opinion
•*Scientific guidances*
Brussels
EU
•MA /administrative decision
•*Pharma. legislation Directives*
Paris
AFSSAPS
Açores (P)
Madeira (P)
Canarias (E)
Guadeloupe (F)
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Malta

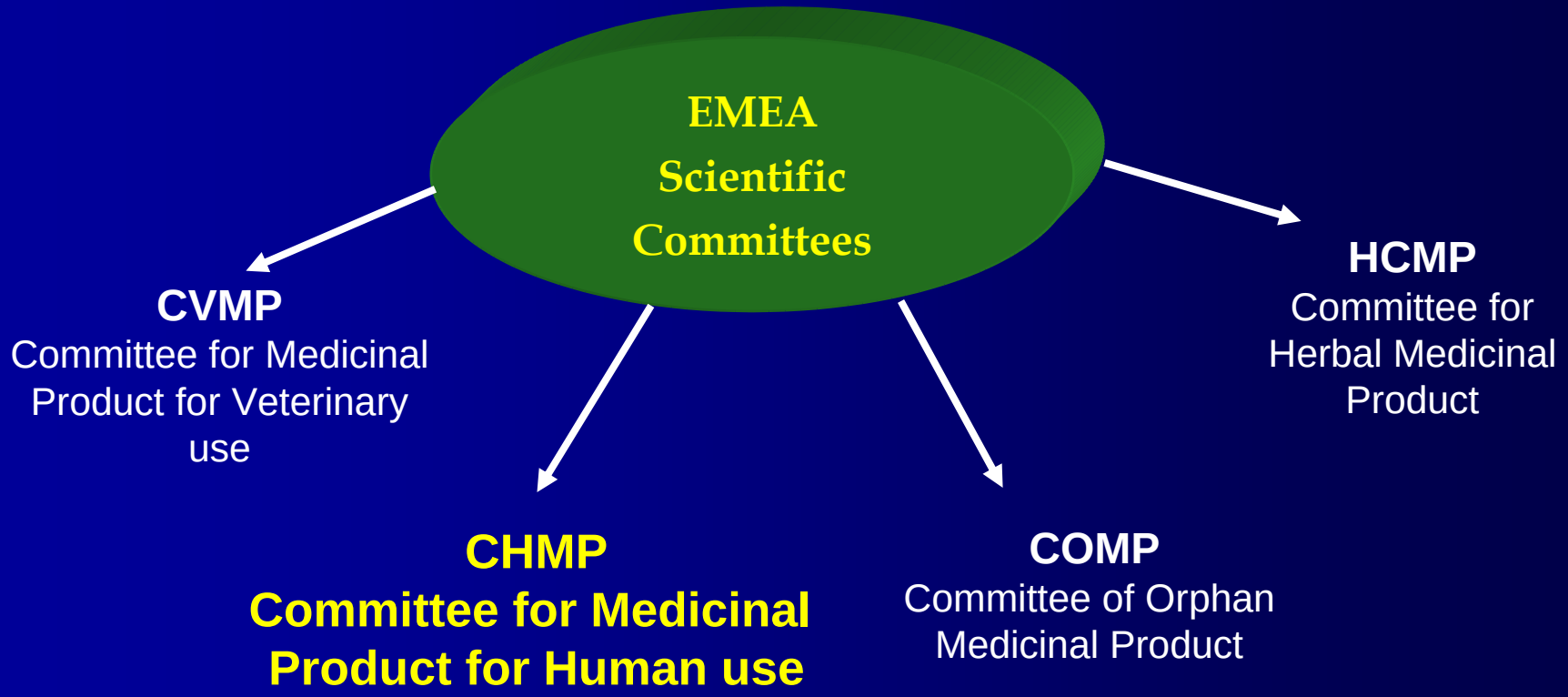
EU Bodies and Procedures

European Medicines Agency (EMEA)

- **1995: European Agency for the Evaluation of Medicinal Products (EMEA)**
- **2004 (EC No 726/2004): European Medicines scientific resources for Agency (EMEA)**
  - Coordinates the evaluation, supervision and pharmacovigilance of medicinal products
  - Scientific resources: 27 member states
  - Over 4000 European experts
  - ~440 staff members

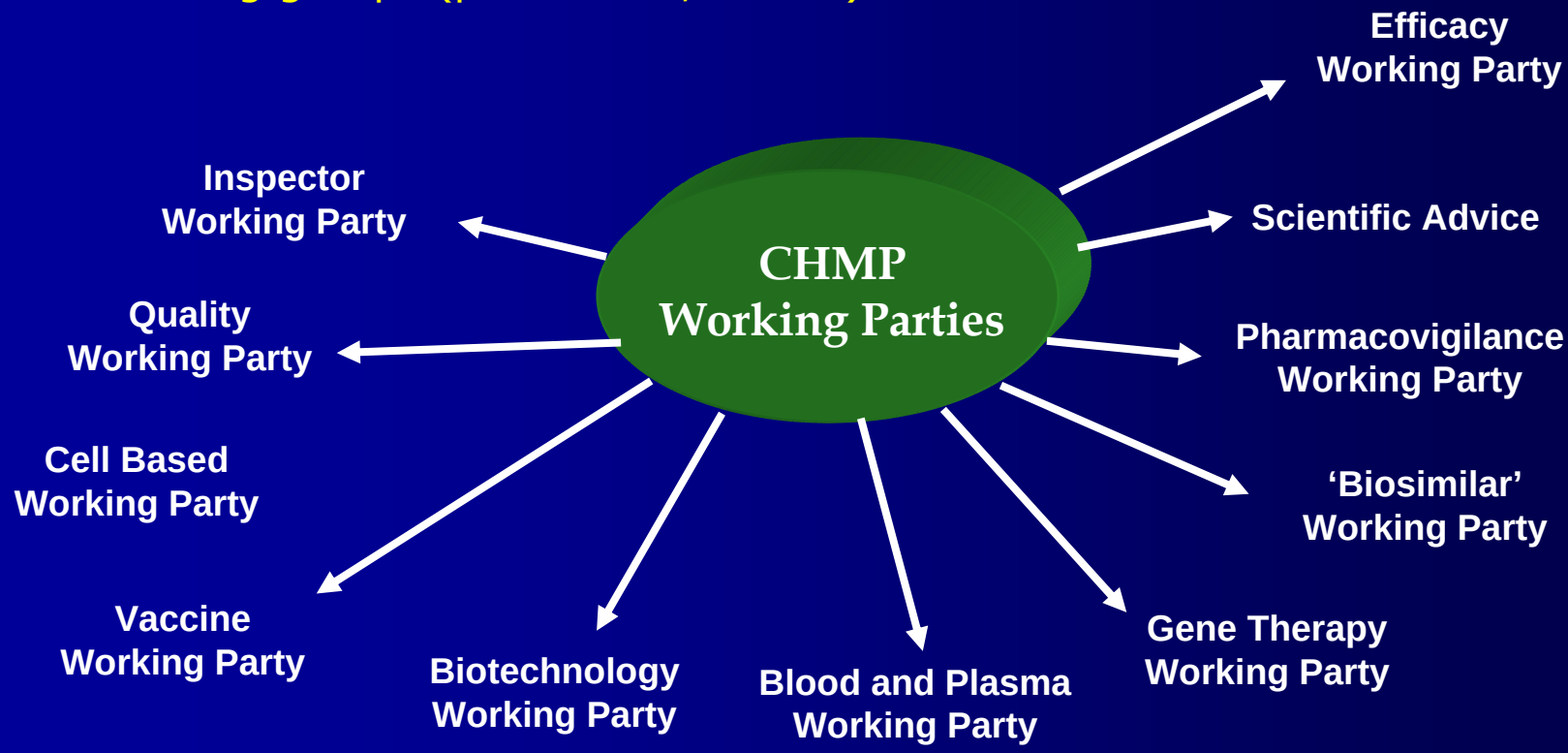
http://www.emea.eu.int/

EU Bodies and Procedures
European Medicines Agency (EMEA)



EU Bodies and Procedures
European Medicines Agency (EMEA)

- **CHMP**
  - Responsible for the scientific opinions (Q, S, E)
  - 1 representative for each member state
  - Chairman (3 years)
  - Working groups (permanent, ad'hoc)



EU Bodies and Procedures
Registration Procedures

	National	Mutual Recognition *Recognition of first country approval*	Centralized
Dossier Submission	**National**	**1 each** **Concerned Member state** *Ex : 6 CMS*	**1** **EMEA**
Scientific Opinion	**National**	**Each member State** *Ex : 4 approvals, 2 rejections*	**CHMP / EMEA (London)**
Administrative Decision	**National**	**National** **Harmonized SPC all EU** *Ex:commercialized in 4+1 MS*	**Eur. Com. (Brussels)** **1 MA all EU** **1 SPC, labelling, package leaflet**

Regulatory environment
Afssaps

Agence française de sécurité sanitaire des produits de santé
(French Health Products Safety Agency)

- National Agency
- ~900 employees
- ~2000 experts

http://afssaps.sante.fr/

Regulatory environment

Afssaps

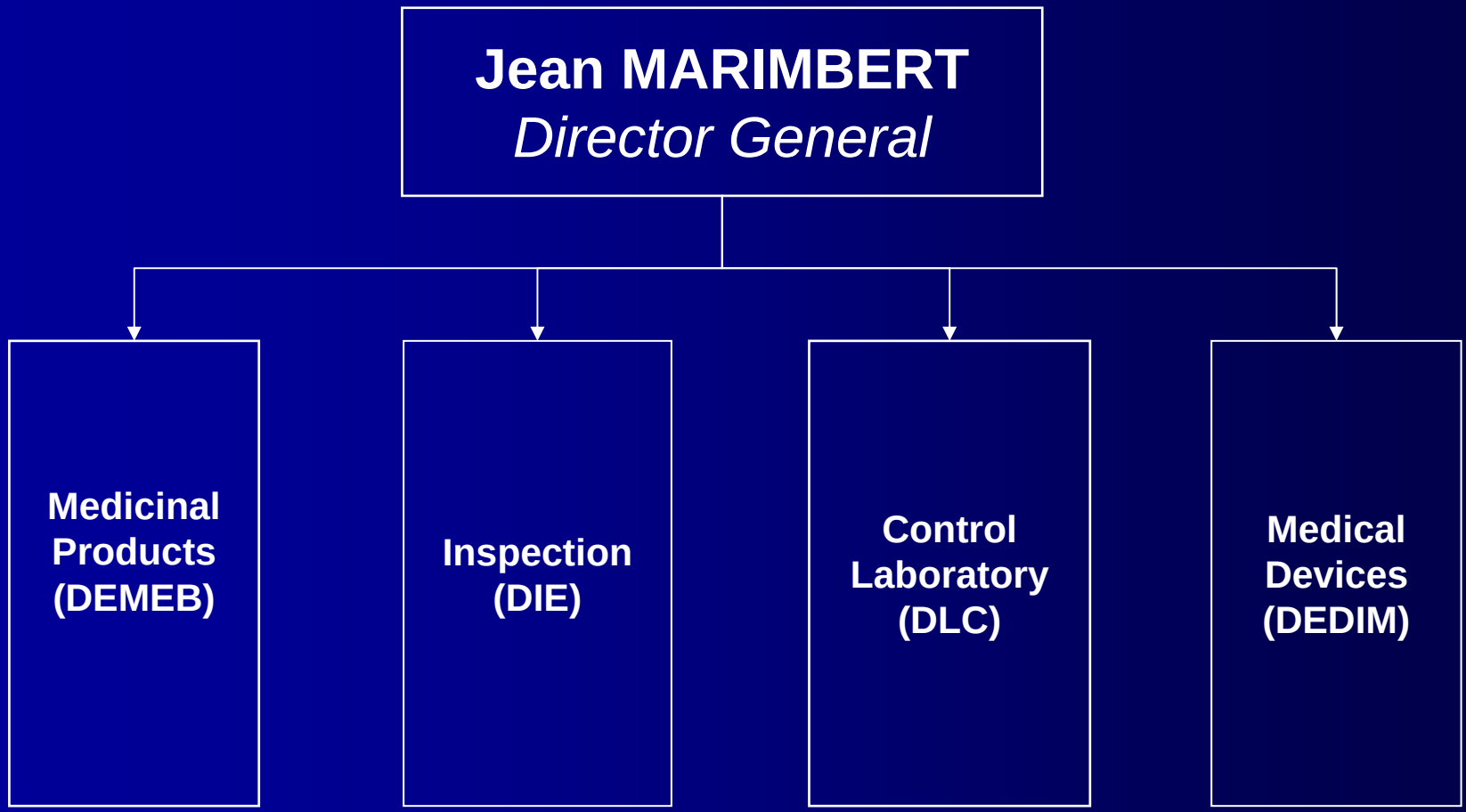
Afssaps
Siège Social et Laboratoires
143/147, boulevard Anatole France
93285 SAINT-DENIS CEDEX
01.55.87.30.00
www.afssaps.sante.fr

Afssaps Laboratoires
321, avenue Jean Jaurès
69007 LYON

Afssaps Laboratoires
635, rue de la Garenne
37740 Vendargues

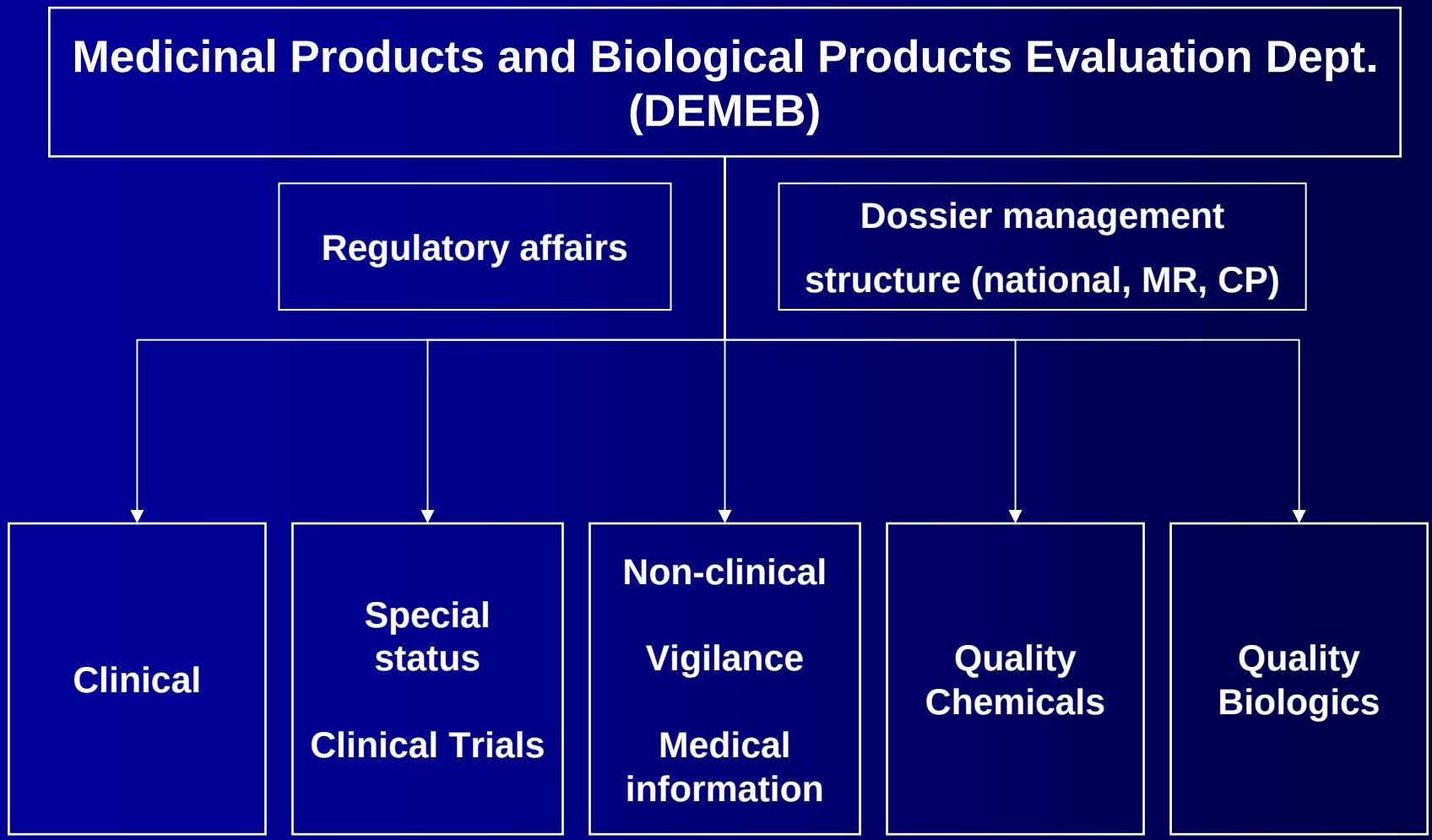
Regulatory environment

Afssaps



Regulatory environment

Afssaps



Similar biological medicinal product

- Biotech specificities

- Legal environment
- Guidelines Q, S & E
- Conclusion

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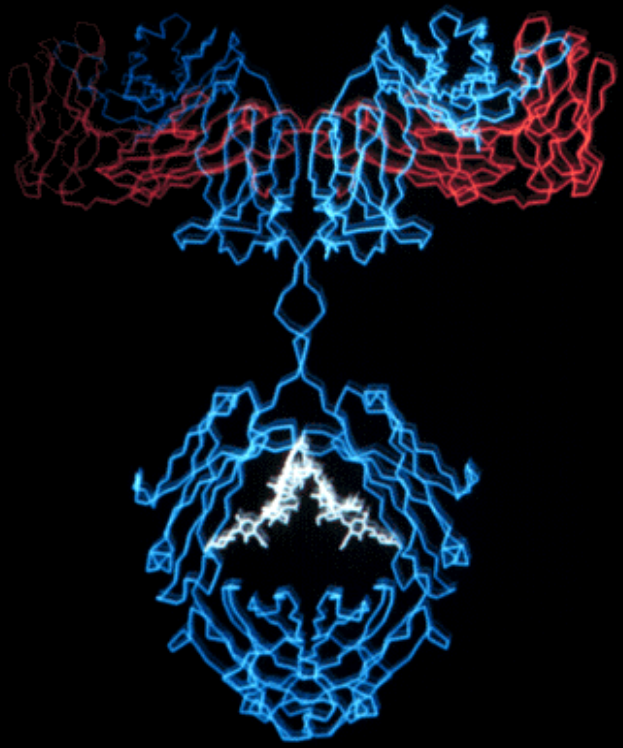
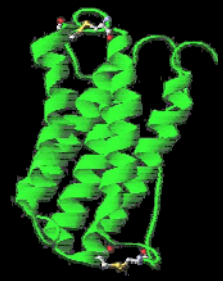
Biotech Specificities
Quality profile



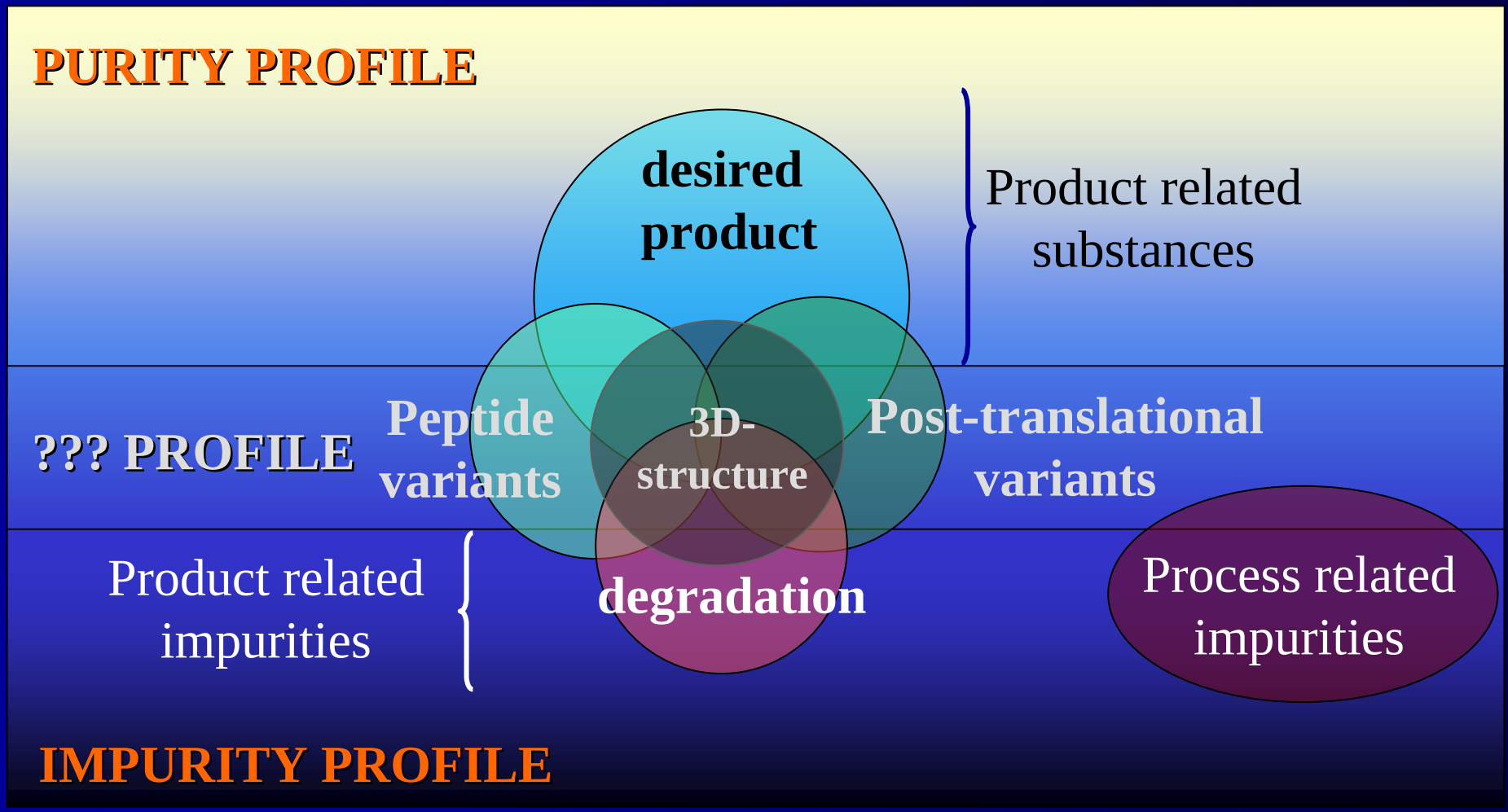
IgG
~660AA, MW: ~150 000 Da



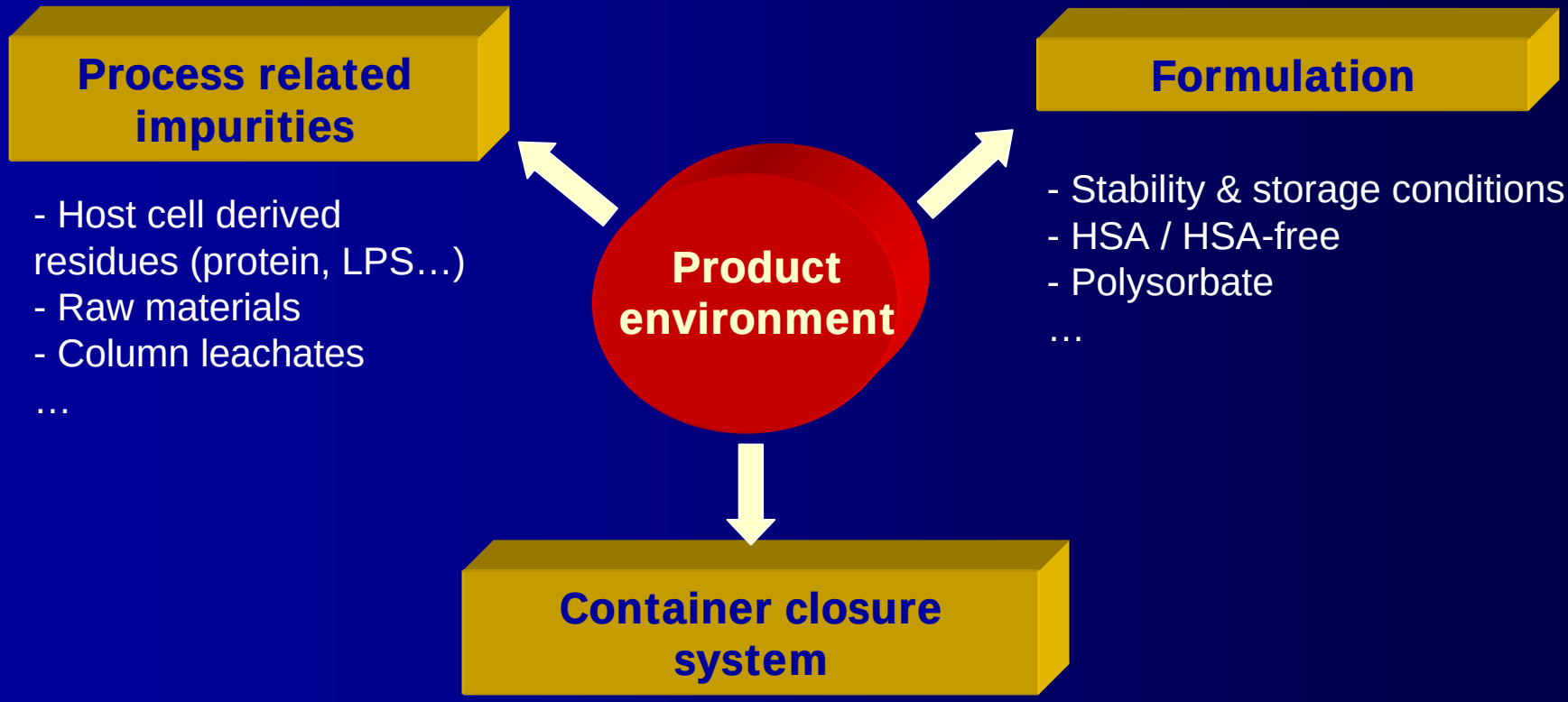
Interferon alfa,
165AA, MW: 19 625 Da

Aspirin,
MW: 180 Da

Biotech Specificities
Quality profile

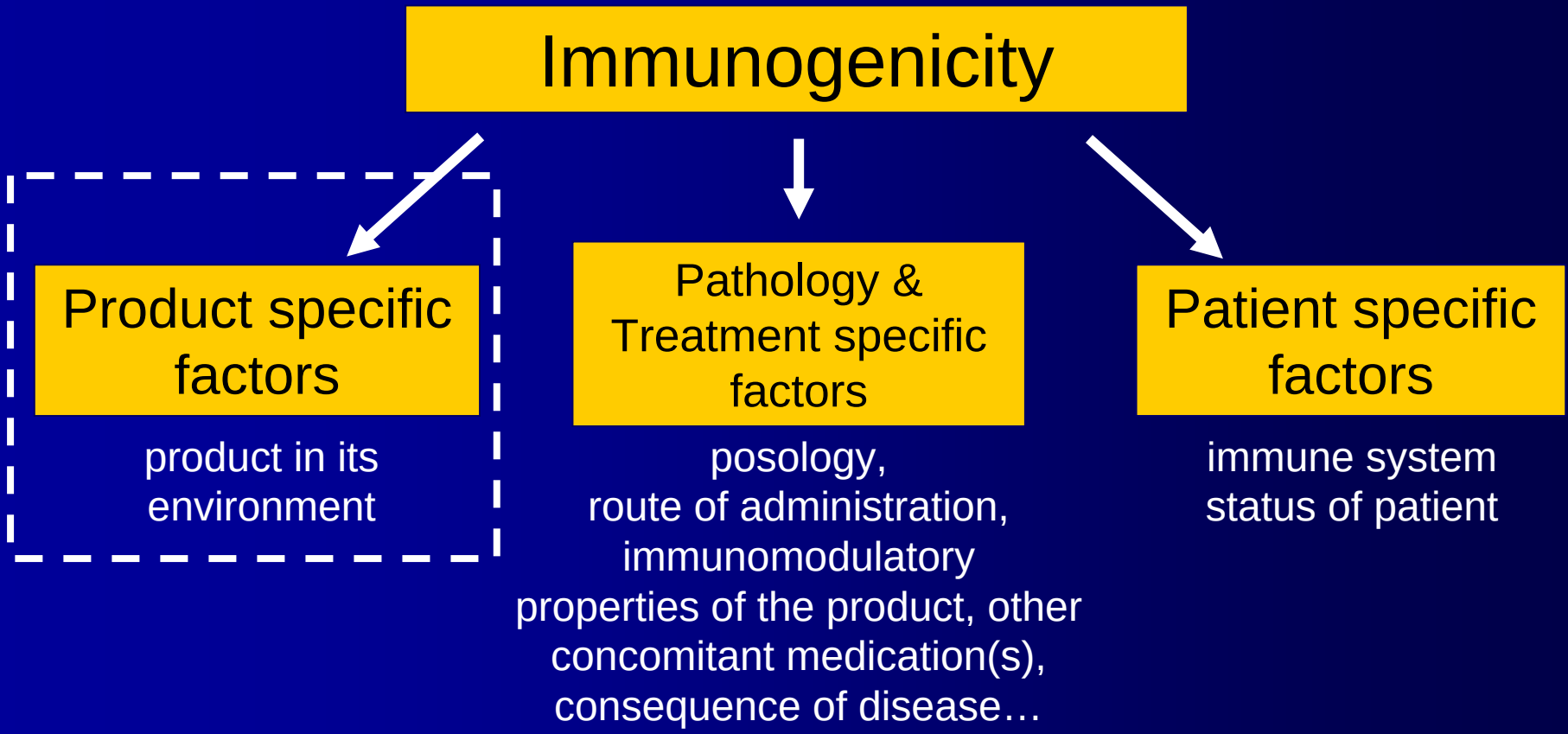


Biotech Specificities
Quality profile

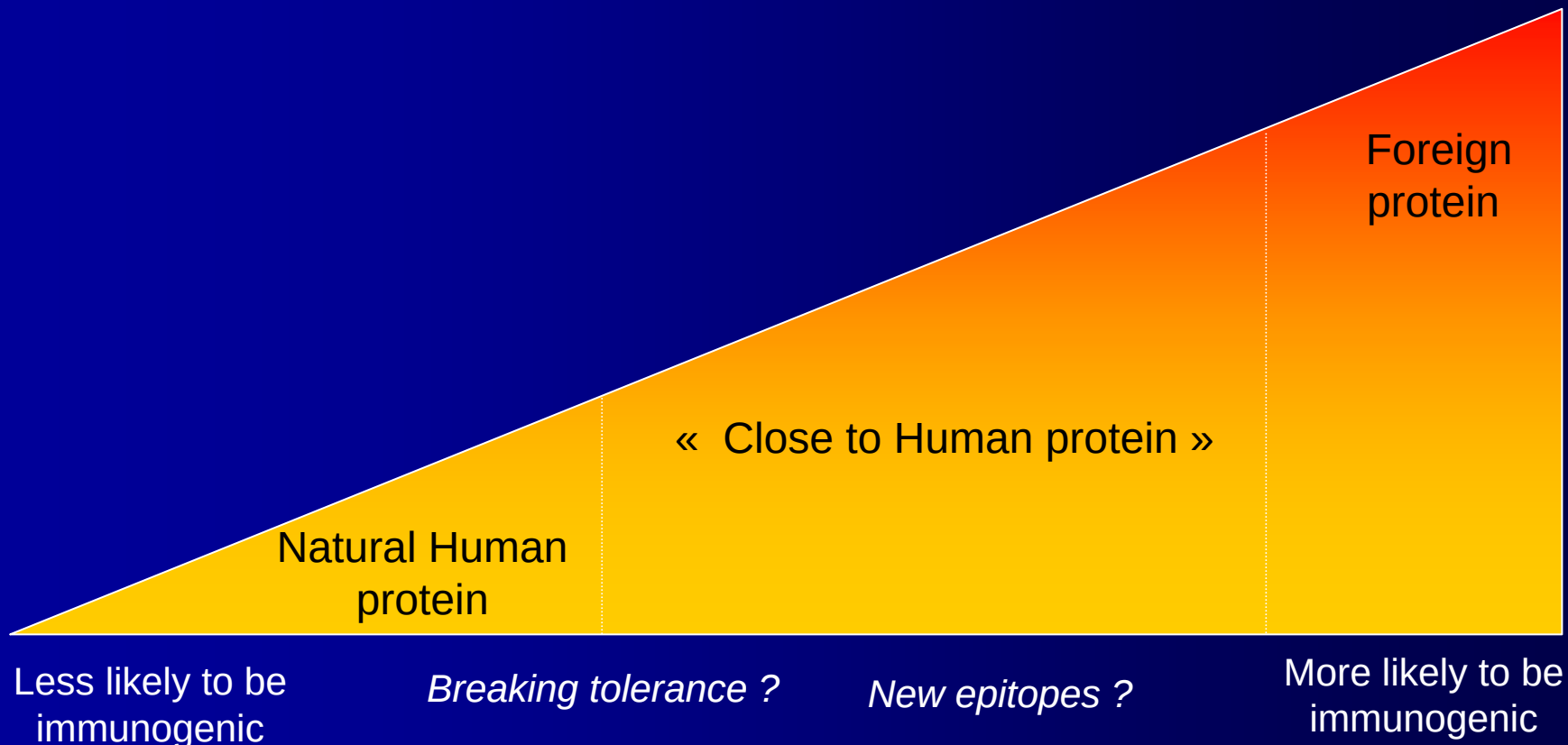


Biotech Specificities

Immunogenicity



Biotech Specificities
Immunogenicity



Biotech Specificities
Analytical & Process considerations

Example 1

- 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

Biotech Specificities
Analytical & Process considerations

Example 2

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

- Formulation and filling
- DRUG PRODUCT

Revision of
manufacturing process
⇧
Significant difference observed
⇧
Change in Host Cell Protein
Detection Kit
(from commercial to process specific)
⇧
IMMUNOGENICITY

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Example 3

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

- Formulation and filling
- DRUG PRODUCT

Change in filling tip

⇩

Increase in aggregates

Biotech Specificities
Analytical & Process considerations

Example 4

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

- Formulation and filling
- DRUG PRODUCT

Change in formulation

⇩

Interaction PS / rubber stopper

⇩

Leachates

⇩

ENHANCED IMMUNOGENICITY ???

Biotech Specificities
"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

Similar biological medicinal product

- Biotech specificities
- Legal environment
- Guidelines Q, S & E
- Conclusion

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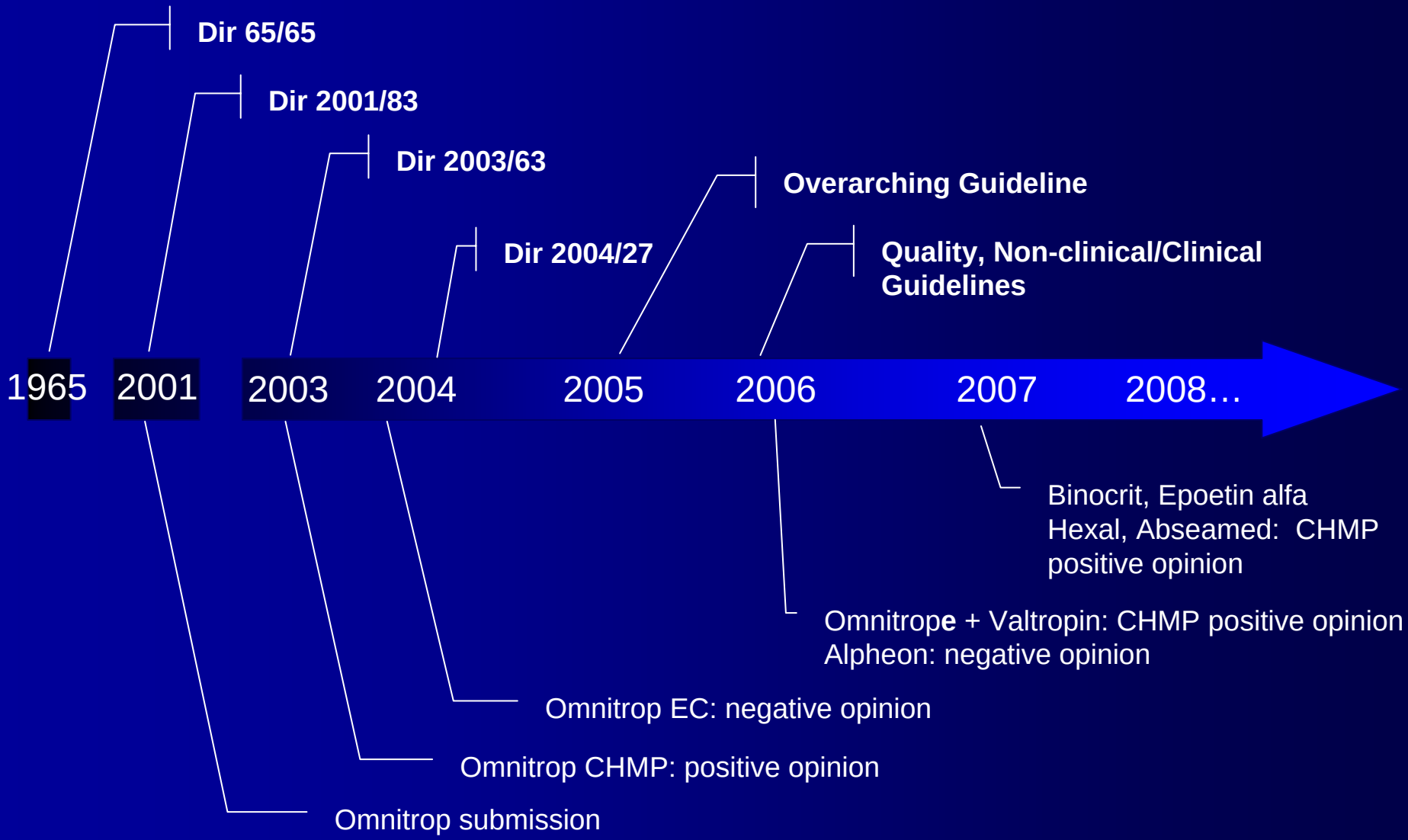
Similar biological medicinal product
Legal environment



Similar biological medicinal product
Legal environment

- **Directive 2001/83/EC, art.10 (1)(a)**
  - (ii) well established medicinal use…
  - (iii)"Essentially similar medicinal product"
    - The applicant must show his product is "essentially similar" to product which has been authorized for not less than 6-10 years in the Community
    - Exemptions for providing the results of toxicological, pharmacological and clinical tests

Similar biological medicinal product
Legal environment

- **Directive 2003/63/EC** (part II):
  - **Essentially similar medicinal products**
    - Essentially similar products (i.e. generics): Modules 1, 2 and 3 + bioavailability and bio-equivalence with the original medicinal product
  - **Similar biological medicinal products**
    - Article 10(1)(a) (iii) may not be sufficient in the case of biological medicinal products.
    - Case by case approach in accordance with relevant scientific guidelines
    - In case the original product has more than one indication : if necessary efficacy & Safety to be demonstrated for each indication

Similar biological medicinal product
Legal environment

- **Directive 2004/27/EC - Article 10:**
  - 2.(b) "generic medicinal product": same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.
  - 4. Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.
  - The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in the Annex and the related detailed guidelines…

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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

Quality
CHMP/BWP/49348/2005:
February 2006

(Non)clinical
Draft 2005 / Adopted 2006

Non-clinical / Clinical
CHMP/BMWP/42832/2005:
Adopted February 2006

Class specific
- Insulin, GH, EPO, GCSF:
Draft 2005 / Adopted 2006
- IFNα, LMWH: ongoing

Insulin — **Non-clin / Clin.**

Somatropin — **Non-clin / Clin.**

Epoetin — **Non-clin / Clin.**

GCSF — **Non-clin / Clin.**

Others… — **Non-clin / Clin.**

** Source: J. Purves, BMWP/BWP training 2007*

Similar biological medicinal product « Overarching guideline »

http://www.emea.europa.eu/htms/human/humanguidelines/multidiscipline.htm

- **CHMP/437/04: adopted September 2005**
- **Introduction of the concept of "similar biological medicinal products"**
  - "Generic approach": not appropriate to biologics due to complexity of molecular structure and/or production
  - Concept could be applied to all biological products
  - Biosimilarity between new and reference product has to be established at all levels: Quality / Security / Efficacy
  - Demonstration of safety and efficacy: requirements product class specific
  - 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

Similar biological medicinal product
Quality

- **CHMP/BWP/49348/2005: Adopted February 2006**
- **Introduction**
  - Comparability exercise at the quality level: reduction of non-clinical and clinical data compared to a full dossier
  - A full quality dossier (CTD Module 3) is required
- **Manufacturing process**
  - Own specific and "state-of–the-art" manufacturing process
  - Molecular composition resulting from its process
  - Own process related impurities
  - Formulation studies should be considered, even if excipients are same as the reference product.
  - Clinical data: manufactured with the final manufacturing process, representing the quality profile of the batches to be commercialized.

Similar biological medicinal product
Quality

- **Comparability Exercise Versus Reference Product**
  - Differences in the quality attributes: to be justified with regard to potential impact on the safety and efficacy
  - Quality attributes: not expected to be identical
  - Comparability at 2 levels: medicinal product + active substance
  - Reference medicinal product must be authorised in the Community
  - The same reference medicinal product must be used for all three parts of the dossier (i.e. Quality, Safety and Efficacy).
  - The shelf life of the reference product should be considered

Similar biological medicinal product
Quality

- **Comparative tests at the level of the active substance:**
  - Comparison to a publicly available standard (i.e. Ph. Eur., WHO, etc.): not appropriate
  - If analyses of the active substance of the reference product can be made at the finished product stage: testing of the isolated active ingredient may not be needed.
  - If analytical tools not be capable of directly comparing the active substance ... should use suitable approaches to isolate representative active substance derived from the reference medicinal product
  - ... demonstrate the suitability of the sample preparation process

Similar biological medicinal product
Quality

- **Analytical methods for similar biological medicinal products**
  - Extensive state-of-the-art characterisation studies in parallel
  - Process-related impurities (e.g., host cell proteins, host cell DNA, reagents, downstream impurities, etc.): Expected to differ qualitatively

- **Specifications**
  - ICH Q6B (based on data obtained from lots used in non-clinical and/or clinical studies, manufacturing consistency, stability studies, relevant development data) + data obtained from the comparability exercise
  - Limits: not wider than the range of variability of the representative reference product

Similar biological medicinal product
Non-clinical / Clinical

- **CHMP/BMWP/42832/2005: Adopted February 2006**

- **Reference product with >1 Indications**
  - Each claimed indication should be justified, or if necessary demonstrated separately
  - Extrapolation to other indication depends on
    - clinical experience
    - available literature data
    - same mechanisms of action or receptor(s) involved in all indications

Similar biological medicinal product
Non-clinical / Clinical

- **Non-clinical studies**
  - Comparative in nature; designed to detect differences
  - In vitro studies:
    - Normally undertaken
    - To assess any possible differences in reactivity
  - In vivo studies
    - Pharmacodynamic effect/activity
    - Non-clinical toxicity: ≥1 repeat-dose including toxicokinetic measurements (including Ab titer, cross reactivity, neutralizing capacity)
  - If specific concerns (e.g. local tolerance) may be addressed in the same repeat dose toxicity study
  - Usually safety pharmacology, reproduction, mutagenicity and carcinogenicity not required

Similar biological medicinal product
Non-clinical / Clinical

- **Clinical studies**
  - Recommended to generate clinical data with the final manufacturing process…
  - Pharmacokinetics (PK) studies
    - Generally, for all routes of administration applied for
    - Absorption and clearance and/or half life (elimination rate may differ)
    - Pre-specified equivalence margins, (acceptance range for generics may not be applicable)
  - Pharmacodynamics (PD) studies
    - Clinically relevant PD marker
    - Combined PK/PD study (information on dose-response relationship)
    - Dose in the linear ascending part of the dose-response curve

Similar biological medicinal product
Non-clinical / Clinical

- Efficacy
  - Confirmatory comparative trial(s) in line with ICH E10 normally required
  - If comparative design not feasible: to be discussed with competent authorities
  - Equivalence margins
    - Pre-specified
    - Adequately justified, primarily on clinical grounds
  - Comparative PK/PD studies may suffice to demonstrate clinical comparability, if
    - PK of the reference product is well characterized
    - Sufficient knowledge of PD properties
    - ≥1 PD marker(s) accepted as surrogate marker(s) for efficacy
    - Equivalence margin appropriately justified
    - Dose-response sufficiently characterised

Similar biological medicinal product
Non-clinical / Clinical

- **Clinical Safety and pharmacovigilance**
  - Clinical data to be provided, even if comparable efficacy
  - Undesirable effects: comparison of type, frequency and severity
  - Not all differences can be detected pre-licensing
  - Risk specification to be provided (including issues related to tolerability)
  - Risk management programme / Pharmacovigilance plan to be provided:
    - Focus on rare adverse reactions
    - Specific PhV measures for the reference product usually to be adopted

Similar biological medicinal product
Non-clinical / Clinical

- **Immunogenicity**
  - Important issue for protein therapeutics
  - Must always be investigated within all clinical trials
    - Cannot be predicted from animal studies
    - Should be considered in different therapeutic indications (i.e. for each indication)
  - Requires validated assay for determination of binding/neutralising antibodies
  - 1 year follow data usually required pre-licensing

Similar biological medicinal product
Non-clinical / Clinical

- **Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues**
  - Erythropoietins - CHMP/94526/05
  - Granulocyte-Colony Stimulating Factor - CHMP/31329/05
  - Somatropin - CHMP/94528/05
  - Human Insulin - CHMP/32775/05
  - Low molecular weight heparins - CHMP/BMWP/496286/06 (draft – comments under review)
  - Interferon alpha – CHMP/BMWP/102046/06 (draft – comments for Apr. 2008)

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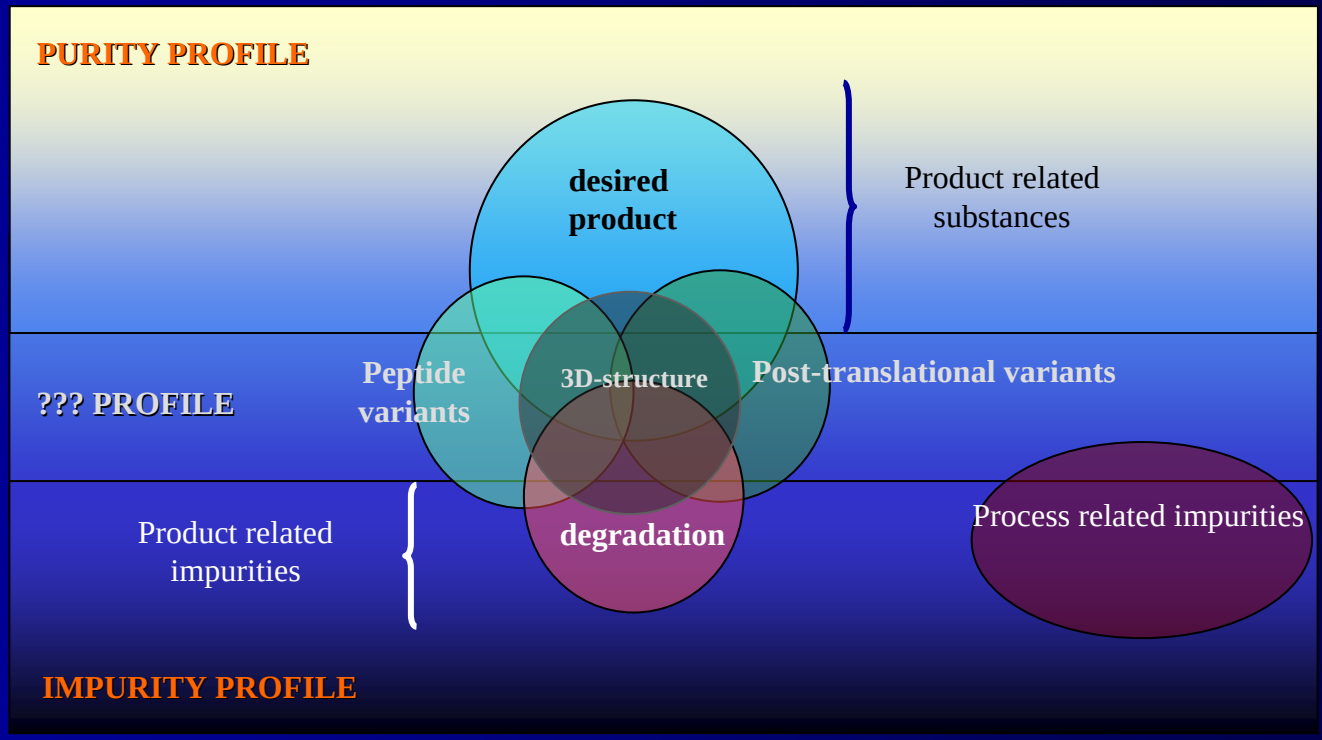
Similar biological medicinal product
Conclusion

- **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)
  - 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
Conclusion

- **Interchangeability / Substitution**
  - Beyond the scope of the current guidelines
  - Not exclusive problem of biosimilars (e.g. Somatropin)
  - National level
  - INN: ongoing challenge...

- **Afssaps' position on substitution:**
  - "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