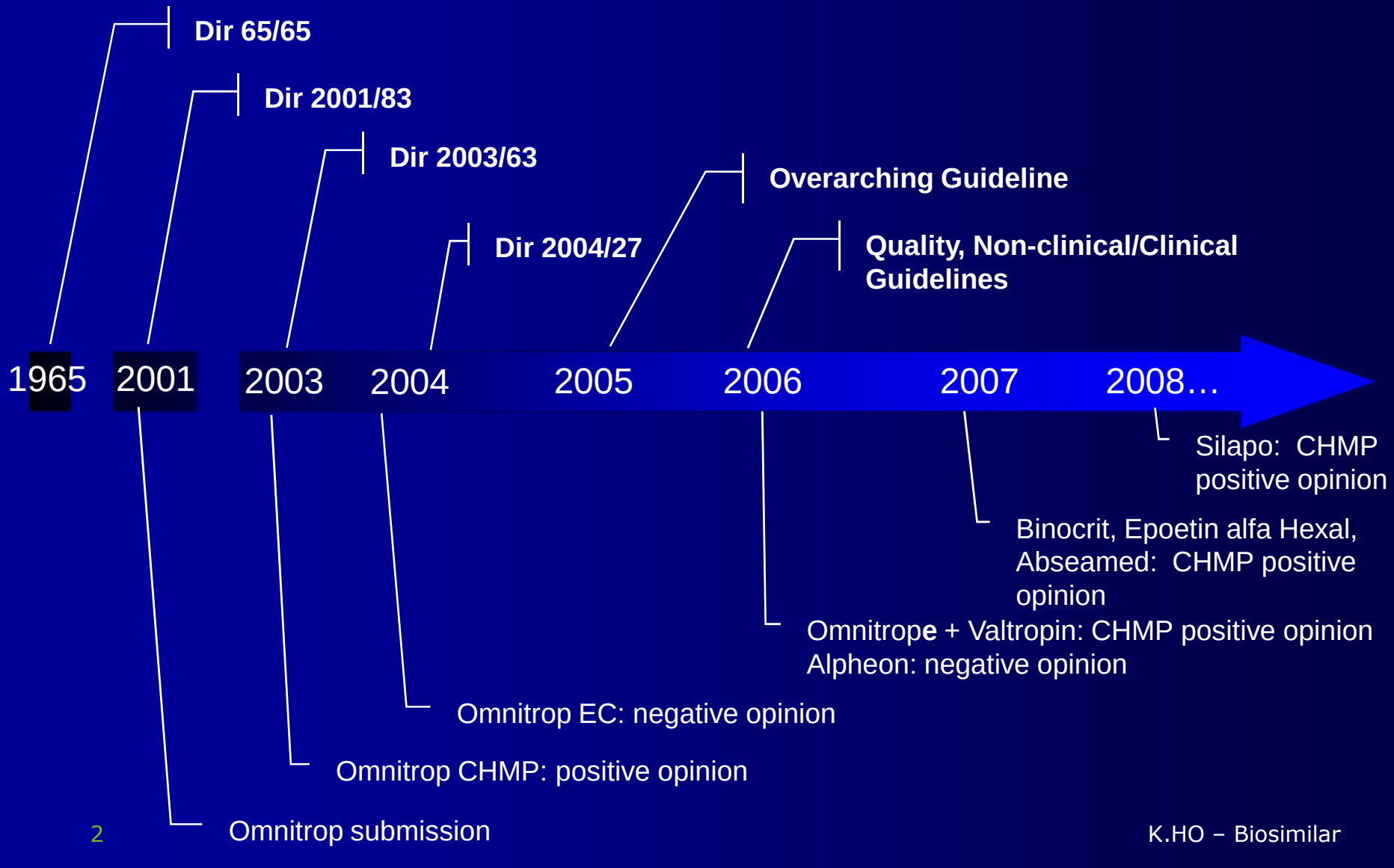
Similar biological medicinal product:
Past and future

Agence française
de sécurité sanitaire
des produits de santé

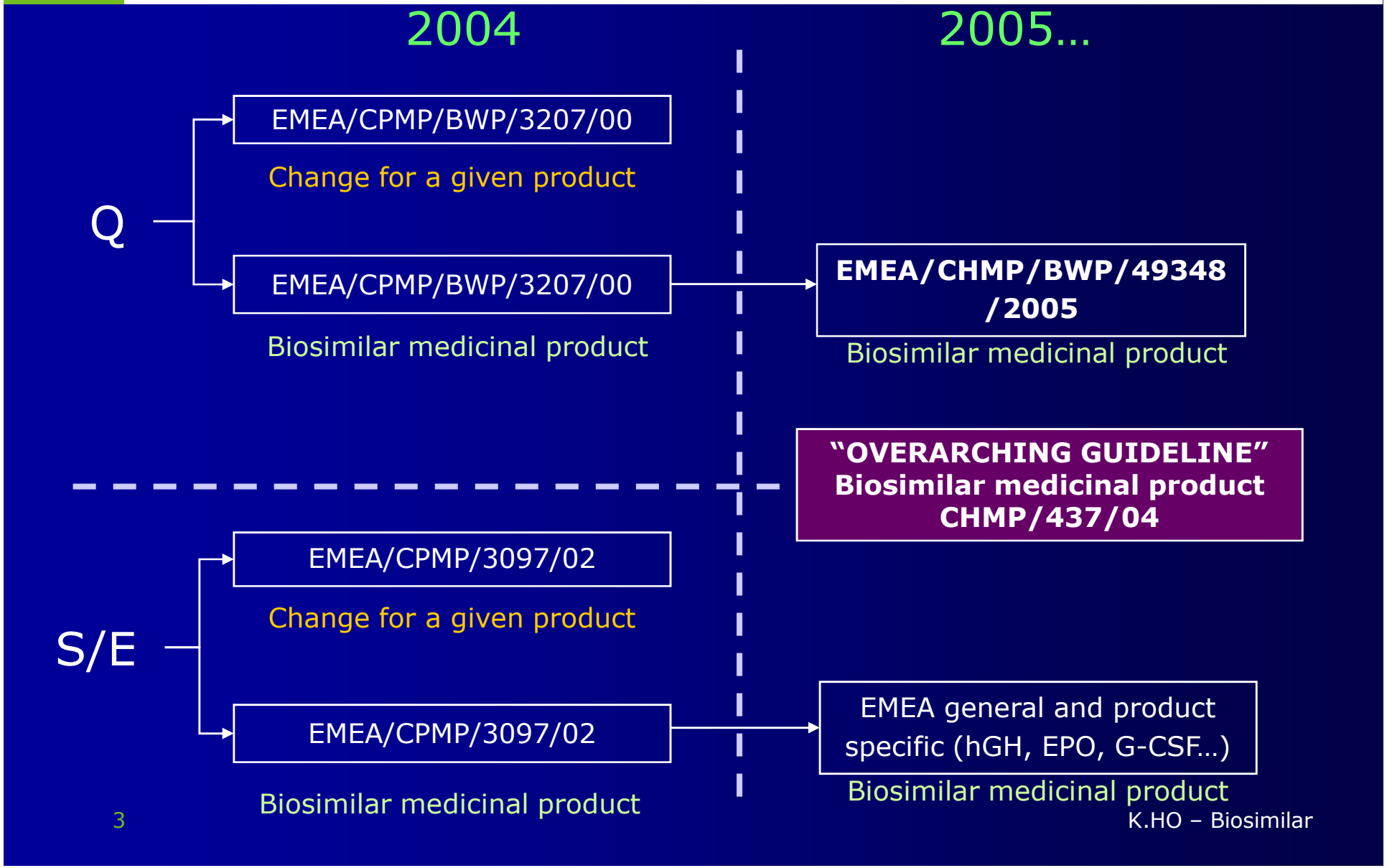
afssaps

K. HO, Biological department

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

Quality

(Non)clinical
Draft 2005 / Adopted 2006

Non-clinical

Clinical

Class specific

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

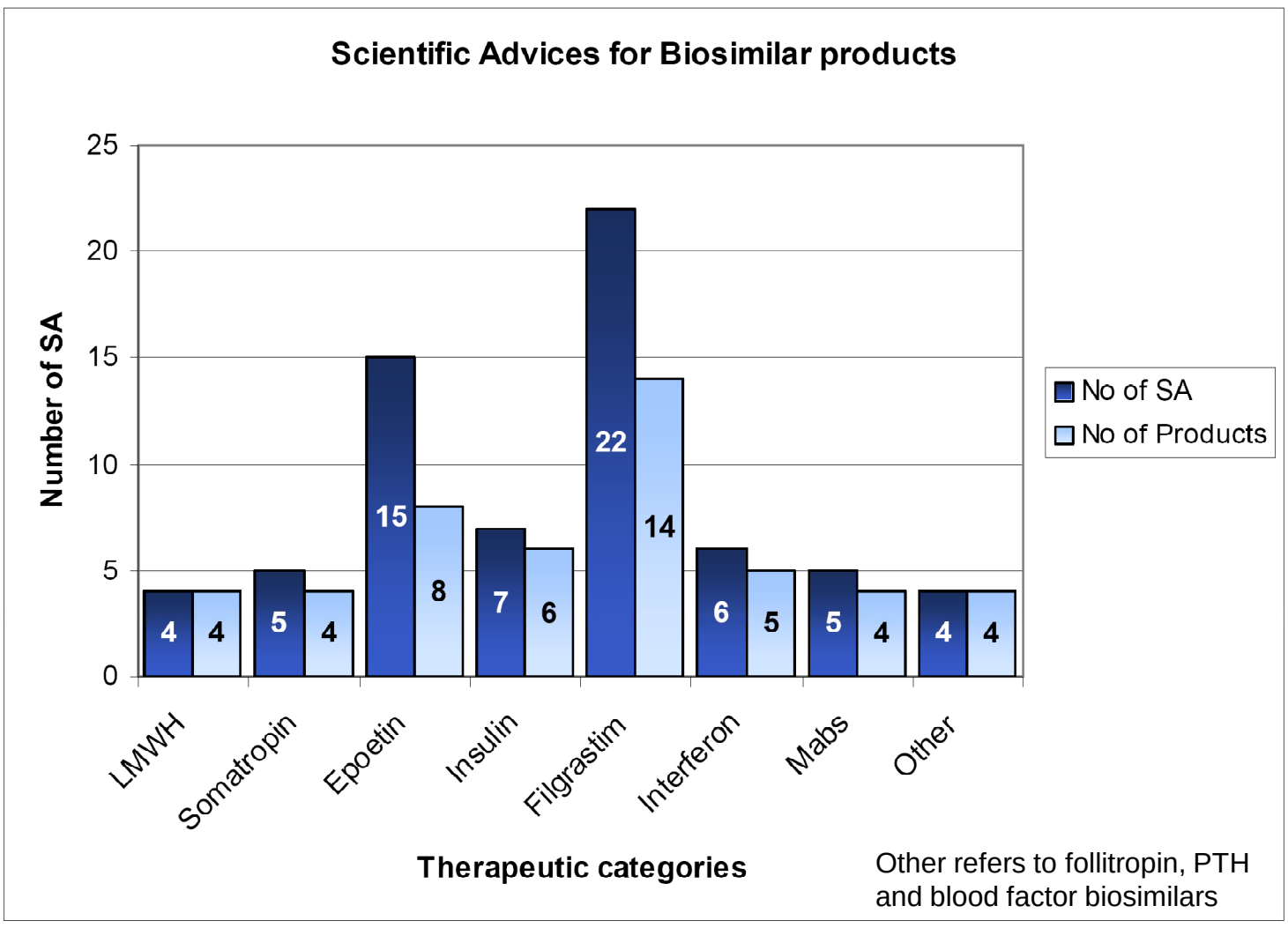
- **Non-clinical / Clinical (CHMP/BMWP/42832/2005)**
  - Clinical Safety and pharmacovigilance
    - Even if comparable: may have different safety profile
    - Pre-authorisation clinical studies: insufficient to identify all potential differences: safety closely monitored post-approval.
      - Risk 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
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
Scientific advices



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

Similar biological medicinal product
EMEA workshop, July 2nd 2009

- **EMEA WORKSHOP ON BIOSIMILAR MONOCLONAL ANTIBODIES**
  - Chairperson: Christian Schneider
  - Discussion on feasibility of the scientific development and authorisation of monoclonal antibodies via the Biosimilar regulatory pathway.
  - 159 people including health care professionals, academics, representatives from regulatory agencies in the European Union (EU), United States (US) and Canada, and 40 biopharmaceutical companies located worldwide attended the workshop. Participation was by invitation only.

Similar biological medicinal product
EMEA workshop, July 2nd 2009

- **EMEA WORKSHOP ON BIOSIMILAR MONOCLONAL ANTIBODIES**
  - 3 sessions:
    1) Chemistry, Manufacturing and Controls (CMC) chaired by Jean-Hugues Trouvin (chair of BWP)
    2) Non-clinical issues chaired by Beatriz Silva-Lima (chair of SWP) and
    3) Clinical issues chaired by Christian Schneider (chair of BMWP)
  - Each session opened with 3 presentations:
    - innovator industry
    - biosimilar/generic industry
    - regulators.
  - Presentations were coordinated by:
    - EBE and EuropaBio for the innovator industry
    - EGA for the biosimilar/generic industry

Similar biological medicinal product
EMEA workshop, July 2nd 2009

- **EMEA WORKSHOP ON BIOSIMILAR MONOCLONAL ANTIBODIES**
  - Sessions 1: Chemistry, Manufacturing and Controls (CMC)
    - Mab = "well characterised" biological?
      - General agreement to avoid the word
    - Quality guidelines: no immediate need for revision or additional annex
    - Current method sensitive enough? Characterisation paradox !
      - Agreement on limitations physico-chemical and biological assays
      - Current tools already detect quality differences, but difficult to link to S/E.

Similar biological medicinal product
EMEA workshop, July 2nd 2009

- **EMEA WORKSHOP ON BIOSIMILAR MONOCLONAL ANTIBODIES**
  - Sessions 1: Chemistry, Manufacturing and Controls (CMC)
    - Can quality data substitute gap in knowledge in functional assay?
      - No, but comprehensive quality data help to mitigate risks
    - How similar should glycosylation be?
      - Can have impact on biological functions
      - Depends on clinical impact
    - Reference product:
      - variability set by the innovator's process, with long experience… can be tight…
      - can evolve… Moving target !

Similar biological medicinal product
EMEA workshop, July 2nd 2009

- **EMEA WORKSHOP ON BIOSIMILAR MONOCLONAL ANTIBODIES**
  - Sessions 1: Chemistry, Manufacturing and Controls (CMC)
    - Role of ICH Q8 and Q9?
      - Important in biosimilar development
      - Specific to a given manufacturer, "design space" not "transferable"

Similar biological medicinal product
EMEA workshop, July 2nd 2009

- **EMEA WORKSHOP ON BIOSIMILAR MONOCLONAL ANTIBODIES**
  - Sessions 2: Non-clinical issues
    - Necessity to perform comparative PK/PD studies; may be combined in 1 study
    - Comparative tox:
      - May not make sense for the purpose of biosimilarity: may not be sufficiently sensitive to see differences
    - Analysis and understanding of MoA: how far to go? signal pathway?
      - Signaling: might be considered in some situation; moving field, science driven, no rigid programme possible… case by case…
    - Impurities: dedicated tox study may not make sense, should be addressed by other tools

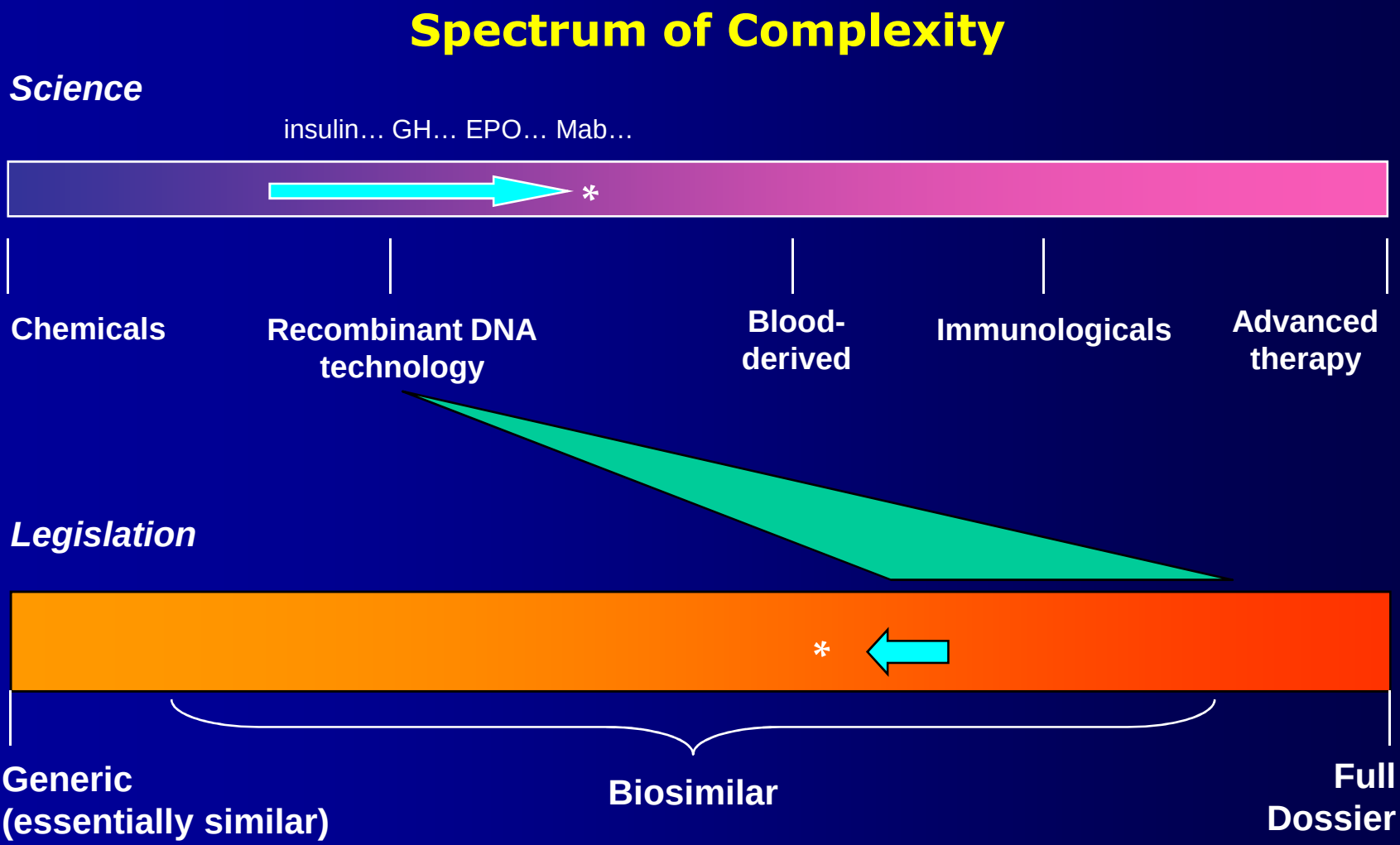
Similar biological medicinal product
EMEA workshop, July 2nd 2009

- **EMEA WORKSHOP ON BIOSIMILAR MONOCLONAL ANTIBODIES**
  - Sessions 3: Clinical issues
    - Agreement that for biosimilarity purpose, the most sensitive population should be selected, and ideally the end point should be clinically relevant.
    - Purpose of that study is not to repeat the innovator pivotal trial.

Similar biological medicinal product
EMEA workshop, July 2nd 2009

- **EMEA WORKSHOP ON BIOSIMILAR MONOCLONAL ANTIBODIES**
  - Conclusion and perspective:
    - Biosimilar approach: basis for 2nd generation products?
      - Current framework can manage 2nd generation products
      - AA difference: industry agreement that should it not be considered as biosimilar
    - Next step:
      - Need for guideline on biosimilar Mab? Quality driven? Class driven?
      - To be discussed at the BMWP, in October 2009…

Similar biological medicinal product
Perspective



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