Clinical Challenges for Establishing Biosimilarity for Monoclonal Antibodies

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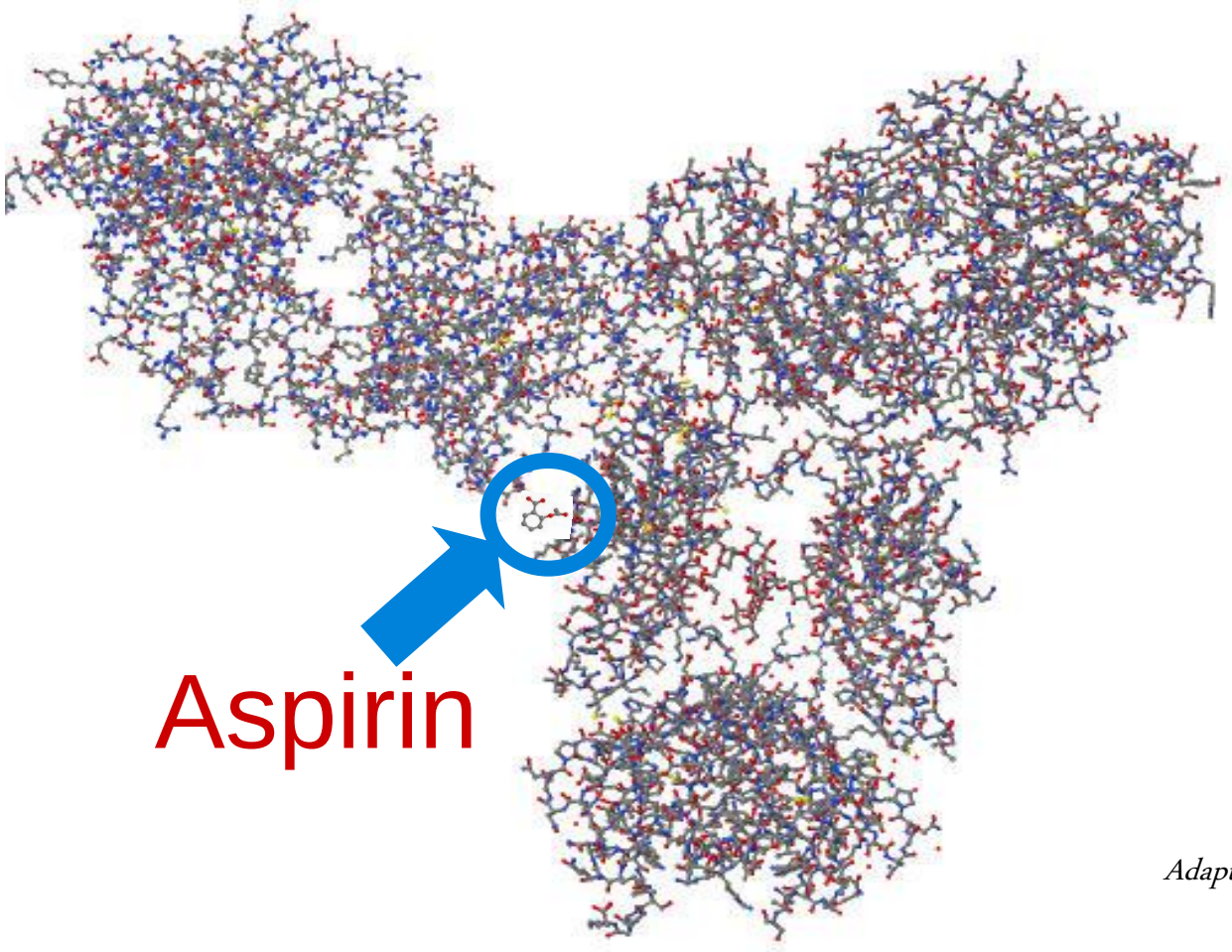
Overview of topics

- Complexity of Biologics - monoclonal Antibodies
- Regulatory environment WHO – EMA – FDA
- Interchangeability. Pharmacovigilance
- Clinical Considerations for Establishing Biosimilarity

Monoclonal Antibody



Adapted from Steven Kozlowski, Director OBP, FDA

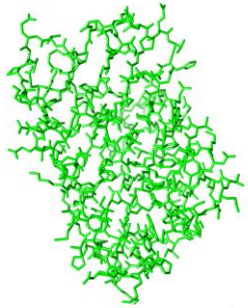
Size, Structure, Complexity

Biological Products are 100-1000 times larger than chemical pharmaceuticals

Aspirin

Molecular weight

= 180 Daltons

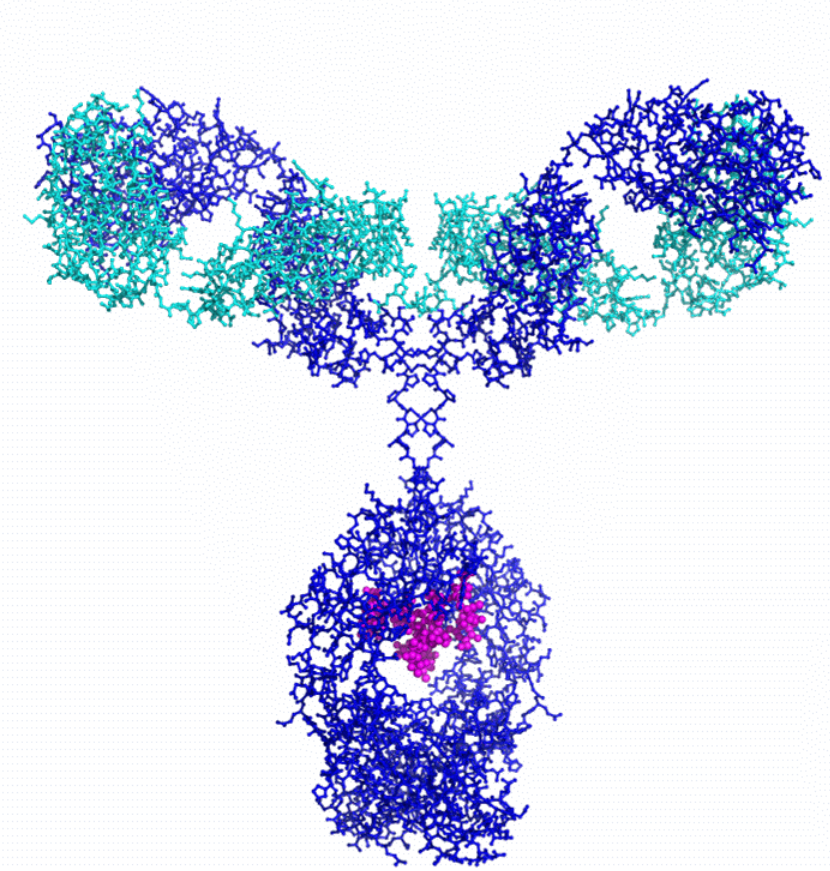


Interferon-alpha

Molecular weight

= 19,625 Daltons

~165 amino acids



Antibody (IgG) molecule

Molecular weight

= 150,000 Daltons

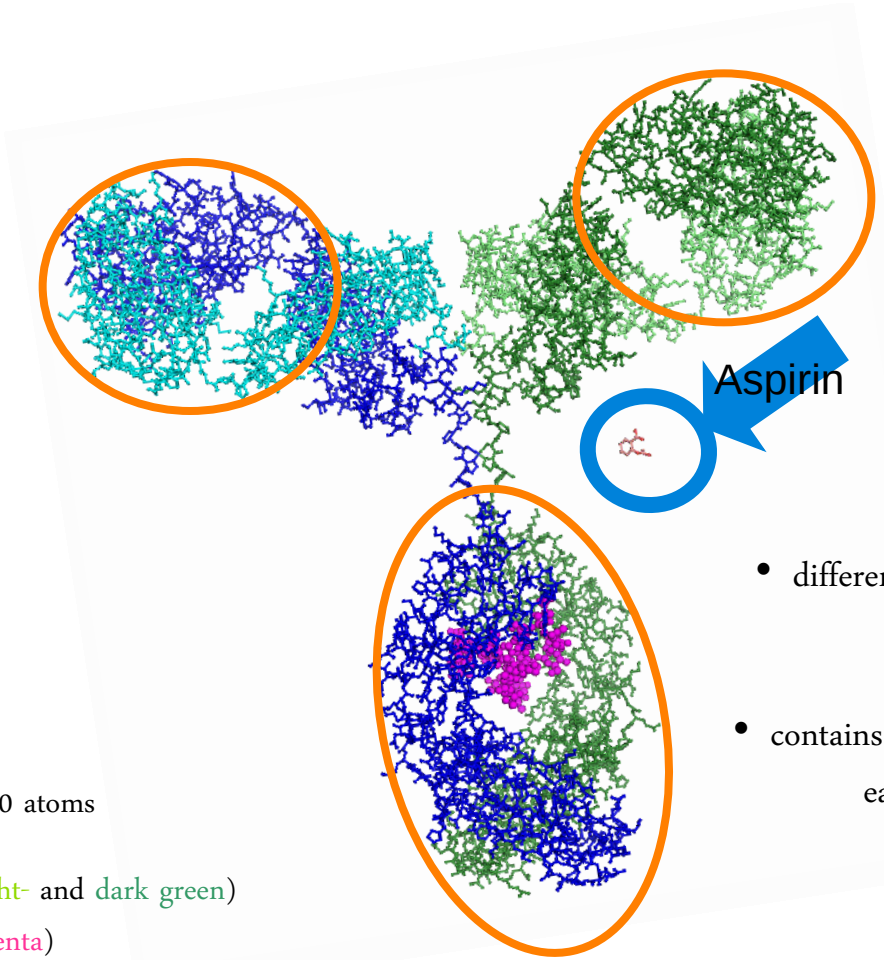
~1,300 amino acids

Images courtesy of Hubert Kettenberger, Roche Penzberg

Monoclonal Antibodies

CDRs (complementarity determining regions)

- selected for optimum target mediated effects (light chain and heavy chain variable binding domains)



Fc part:

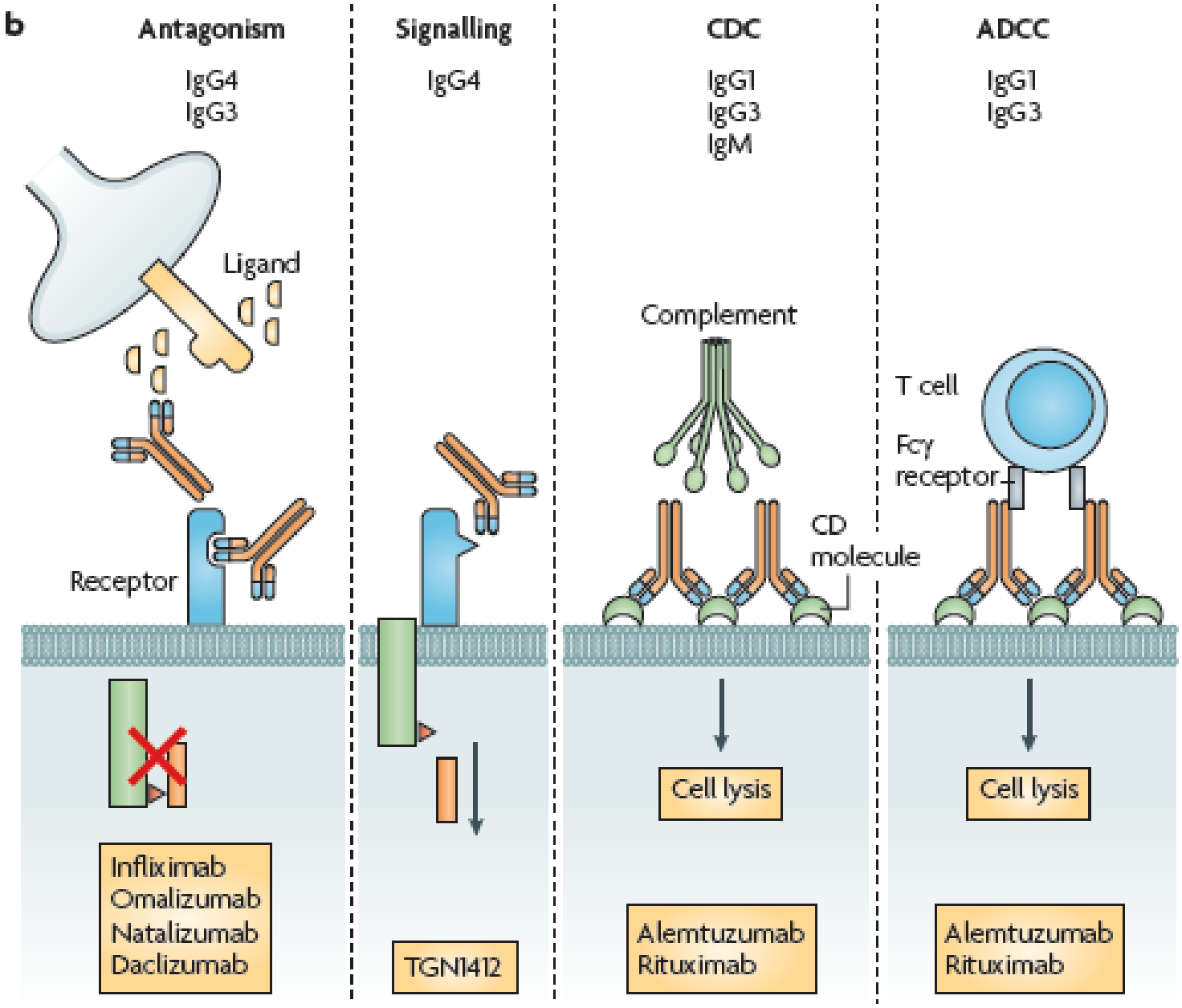
- different isotypes with different effector functions
- contains 2 glycosylation sites (1 in each of the 2 chains)

- In total more than 20.000 atoms
- 4 subunits (light- and dark blue, light- and dark green) + carbohydrate (magenta)
- **all parts contribute to the efficacy and safety in a cooperative way**

- $(9600)^2 \approx 10^8$ potential variants

IgG1 molecule according to EA Padlan (1994)
Courtesy of Hubert Kettenberger, Roche Penzberg

Monoclonal Antibodies - different mode of actions



Hansel, Kropshofer, Singer, Mitchell & George

Nature reviews drug discovery

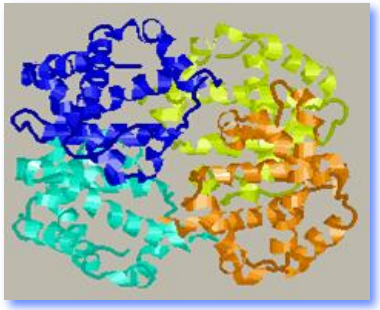
22.March 2010

Biological Products: Complexity

- The complexity of Biological Products makes identical copies impossible

Inherent Complexity

- Size
- Structure
- Physicochemistry
- Heterogeneity

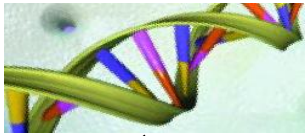


Added Complexity

- Manufacturing process
- Formulation
- Handling
- Route of Administration

Biosimilar Manufacturing

The process is the product



Same gene as innovator

Differences in the process

Human gene

DNA vector

Cloning into DNA vector

Transfer into host cell

Bacterial or mammalian cell produces protein

Fermentation

Formulation

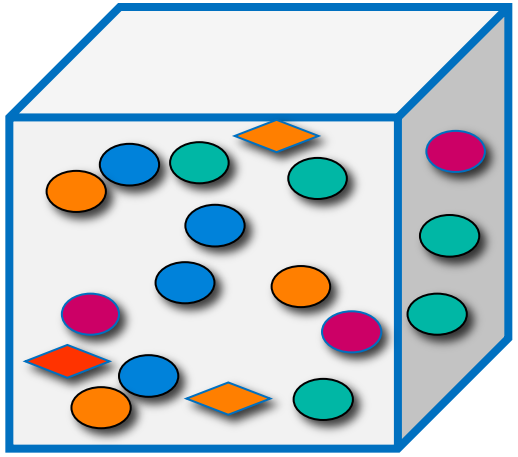
A Biosimilar is different from the originator

Even if a biosimilar uses the same human gene as its innovator, it will differ in other parts of the manufacturing process

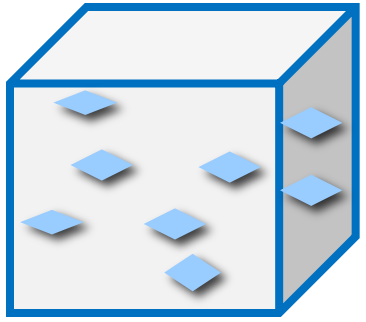
Biopharmaceuticals – Heterogeneity

- Biotech products are very complex, sensitive, heterogeneous mixtures of protein molecules
- Each molecular entity of that mixture is characterized by specific physical, chemical and biological properties
- Any change in the composition of that mixture could affect patient safety and efficacy

Molecular Heterogeneity



Large Molecule



Small Molecule

What are Biosimilars and What Regulates their Development?

Biologics/Biosimilars Manufacturing

The proprietary process is the product

Generics

Follow-on products of traditional chemical pharmaceuticals are exact chemical copies

Relatively easy to reproduce exactly

Biosimilars

Similarity has been shown in terms of quality, safety and efficacy to the originator

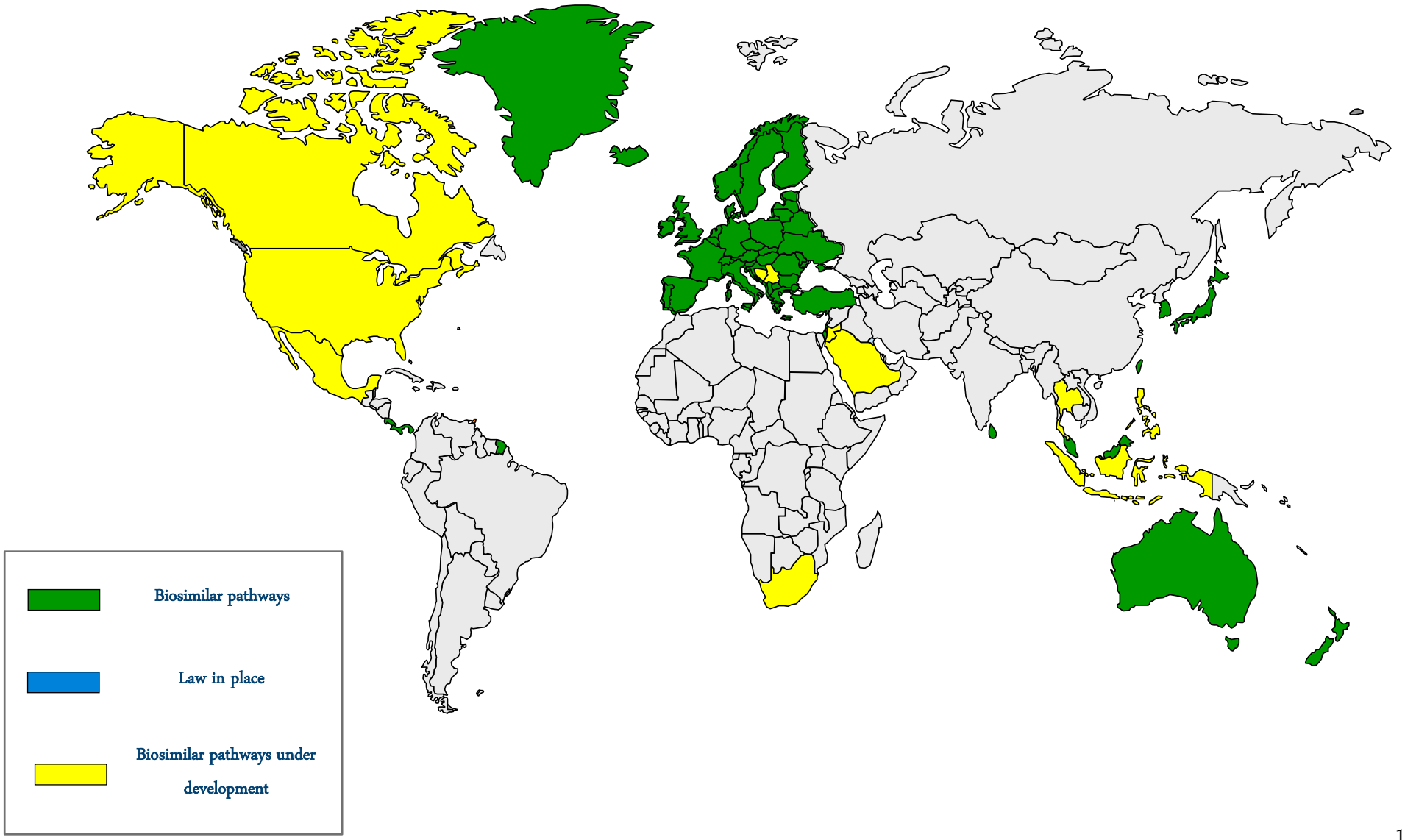
There are no 'bio-generics', there are only similar products

Manufacturing based on unique cell lines

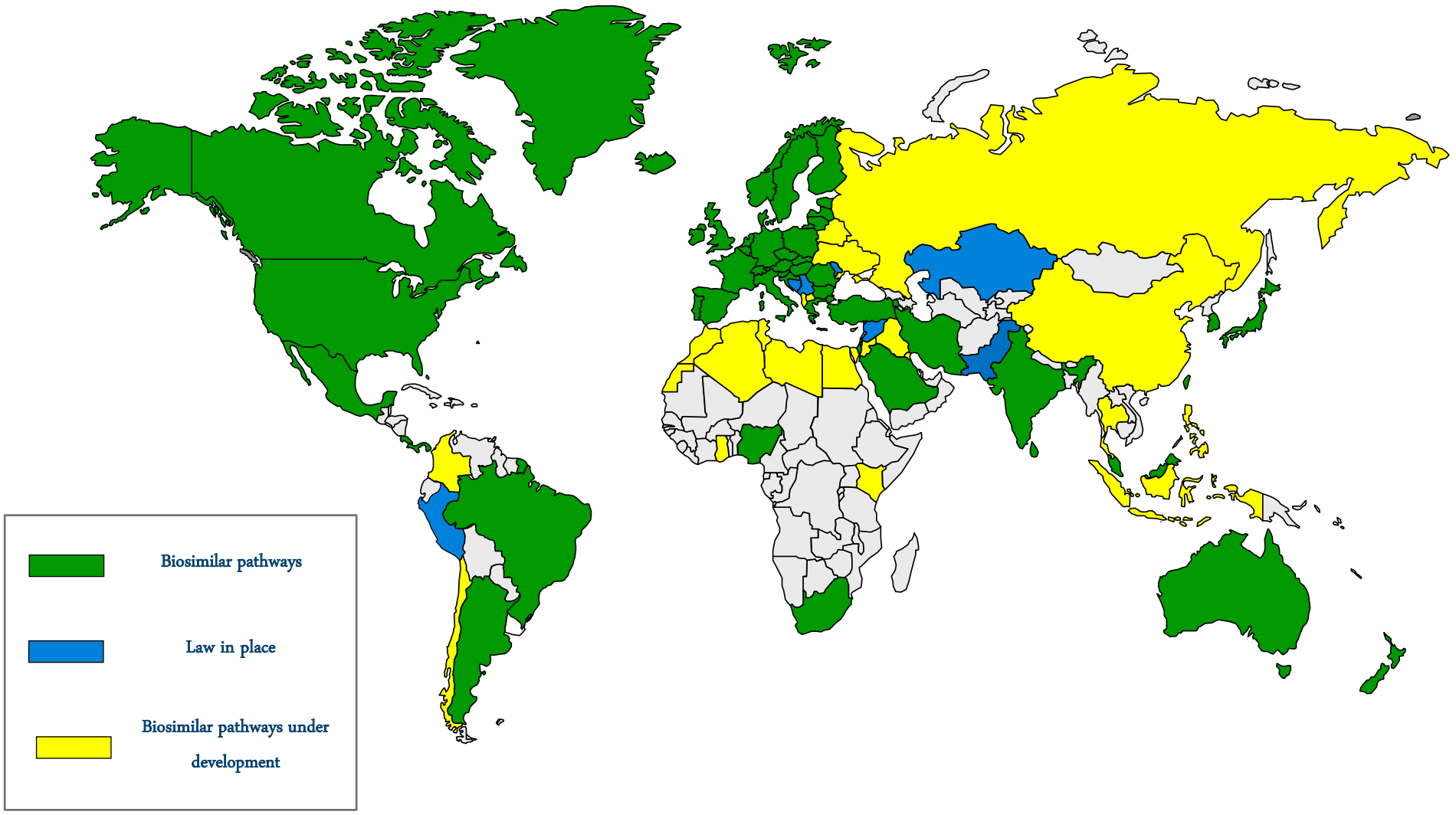
Processes are very complex and difficult to reproduce

Changes may lead to different clinical **efficacy** and **safety**

Biosimilar Pathways | How advanced were we before 2010?



Biosimilar pathways - where are as of February 2013



Updated 11th February 2013

WHO:

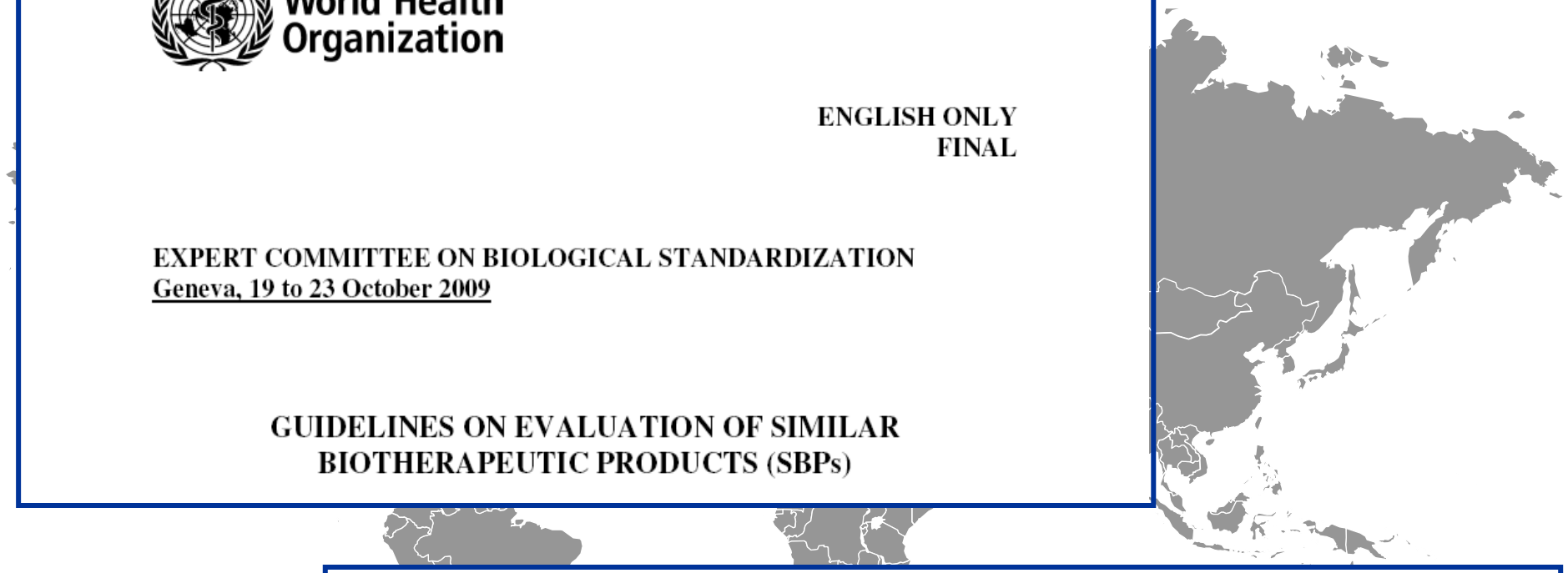
Global standard for robust biosimilar pathway

World Health Organization

ENGLISH ONLY
FINAL

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 19 to 23 October 2009

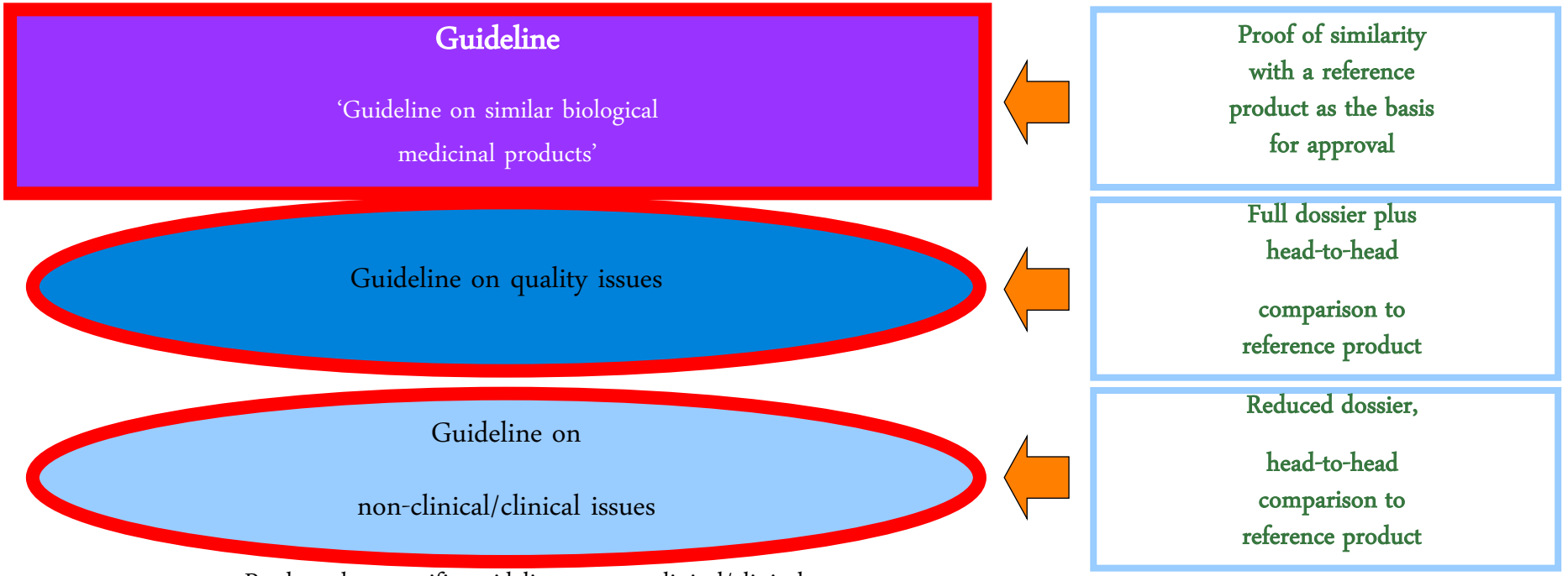
GUIDELINES ON EVALUATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS (SBPs)



2 Aim

The intention of this document is to provide globally acceptable principles for licensing biotherapeutic products that are claimed to be similar to biotherapeutic products of assured quality, safety, and efficacy that have been licensed based on a full licensing dossier. On the basis of proven similarities, the development of SBP will rely, in part, on non-clinical and clinical data generated an already licensed product on the reference biotherapeutic product (RBP).

EMA
Biosimilar guidelines



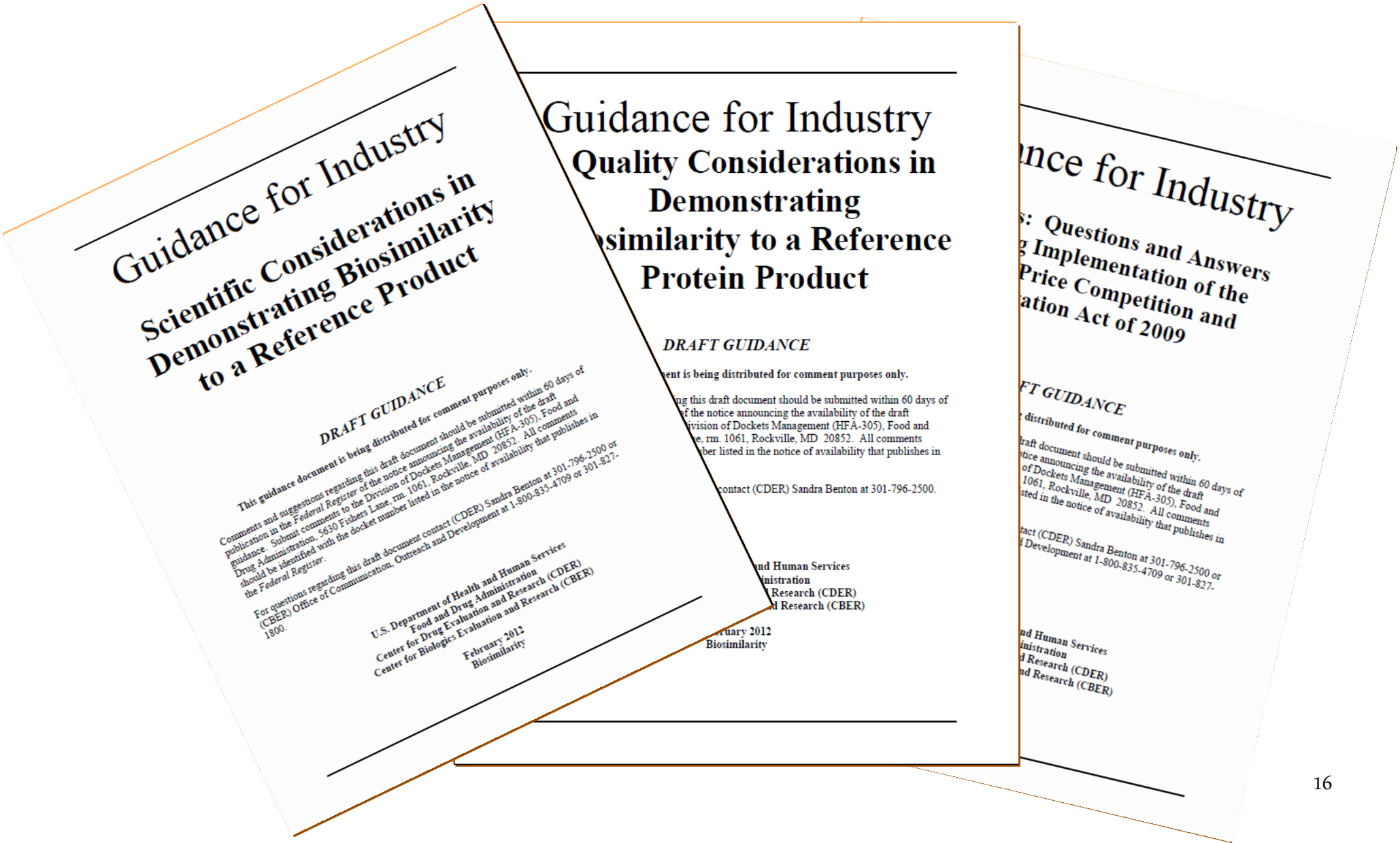
Product-class specific guidelines on nonclinical/clinical:

Insulin | LMWH | G-CSF | Epoetin | IFN-alpha | GH

Product specific – guidelines under development

IFN-beta | *FSH* | mAbs

FDA Biosimilar Draft Guidances



Substitution/Interchangebility Pharmacovigilance

Key concern - Immunogenicity:

- **Neutralizing antibodies** → impact on therapeutic effect
  - coagulation factor concentrates (eg, Factor VIII and Factor IX),
  - enzyme replacement therapies (eg, acid-α-glucosidase and glucocerebrosidase),
  - hormones (eg, GH)
  - cytokines (eg, GM-CSF and IFNβ)
- **Hypersensitivity reactions**
- **Cross-reactivity** with an endogenous protein that has a vital, non-redundant biological function
  - PEGylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF),
  - PRCA with epoetin alfa

Wadhwa, Idrugs, 2009

Immunogenicity of Biosimilars:
Monitoring the risk

- In order to demonstrate the safety and efficacy of a biosimilar, regulatory authorities and experts agree on the need for pre-authorisation data
  - Non-clinical data
  - Clinical data (including immunogenicity testing)
- Risk must be assessed with adequate number of patients and clinical studies of appropriate duration
- However, immunogenicity remains unpredictable

Safety of Biosimilars: Pharmacovigilance

- A post-authorisation risk management programme is necessary to ensure proper evaluation of the risk/benefit profile of a biosimilar
- Such a programme must include:
  - Continuous immunogenicity testing
  - Pharmacovigilance monitoring
- Unique identification of a biosimilar product is essential (i.e. a brand name)
- The marketing and utilization of biosimilar antibodies must not enable automatic substitution with a reference product without the consent and supervision of a qualified physician
- Labelling for biosimilar antibodies must clearly identify the sources of the specific clinical safety and efficacy data obtained during its development (e.g. extrapolation, originator's data, data of the biosimilar)
- Biosimilar antibody products should have **unique identity or name** and **prescriptions be made by brand name, allowing traceability to the patient level**

EMA Regulations and Interchangeability

- ‘Switching’ and ‘interchanging’ of medicines that contain a given mAb might occur. Thus, applicants are recommended to follow further development in the field and consider these aspects as part of the risk management plan. *(Final EMA MoAb Guidance June 2012)*

FDA View on Interchangeability from Draft Guidance on Biosimilars (Feb 2012)

- An interchangeable product must be shown to be biosimilar to the reference product and meet the other standards described in section 351(k)(4) of the PHS Act.

- At this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment.

- FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product

Clinical Considerations:

Differences in requirement and study design for biosimilars vs innovator, Extrapolation

Biosimilar vs. innovator clinical studies in oncology. Differences on requirement and study design

Aspects of Development	Biosimilar	Innovator
Patient Population	Sensitive and homogeneous (patients are *models*)	Any
Clinical Design	Comparative versus innovator, normally equivalence	Superiority vs standard of care (SoC*)
Study Endpoints	Sensitive Clinically validated PD markers	Clinical outcomes data or accepted/established surrogates (e.g. OS and PFS)
Safety	Similar safety profile to innovator	Acceptable risk/benefit profile versus SoC*
Immunogenicity	Similar immunogenicity profile to innovator	Acceptable risk/benefit profile versus SoC*
Extrapolation	Possible if justified	Not allowed

* In some cases SoC may not exist

Neo-Adjuvant/Adjuvant is an homogeneus and sensitive population to establish similarity for a trastuzumab (Herceptin®) biosimilar

Topic	Metastatic (palliative)	Neo-Adjuvant/Adjuvant (curative)
PK	(-,+) Affected by patients status and tumour burden	(-,+) Homogeneous population can be selected
PD	(-) Clinically validated PD marker not available	(-) Clinically validated PD marker not available
Clinical Efficacy/Safety	(-) Population with heterogeneous characteristics affecting final clinical outcome. Need to control and stratify for multiple factors (e.g. prior use of chemotherapy, performance status,...). Difficult to select an homogeneous group	(+) Baseline patient characteristics allow to select homogeneous populations not confounded by external factors
Immunogenicity	(-) Immuno compromised patients with immune system affected by performance status and concomitant chemotherapies received	(+) Immune system impaired during chemotherapy cycles, but would likely recover to *normal* status after that period

Extrapolation of indications – EMA view

6. Extrapolation of Indications

Extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, is possible based on the overall evidence of biosimilarity provided from the comparability exercise and with adequate justification. If pivotal evidence for biosimilarity is based on PD and for the claimed indications different

If a reference mAb is licensed both as an immunomodulator and as an anticancer (cytotoxic) antibody, the scientific justification as regards extrapolation between the two (or more) indications is more challenging. The basis for such extrapolation forms an extensive quality and non-clinical database,

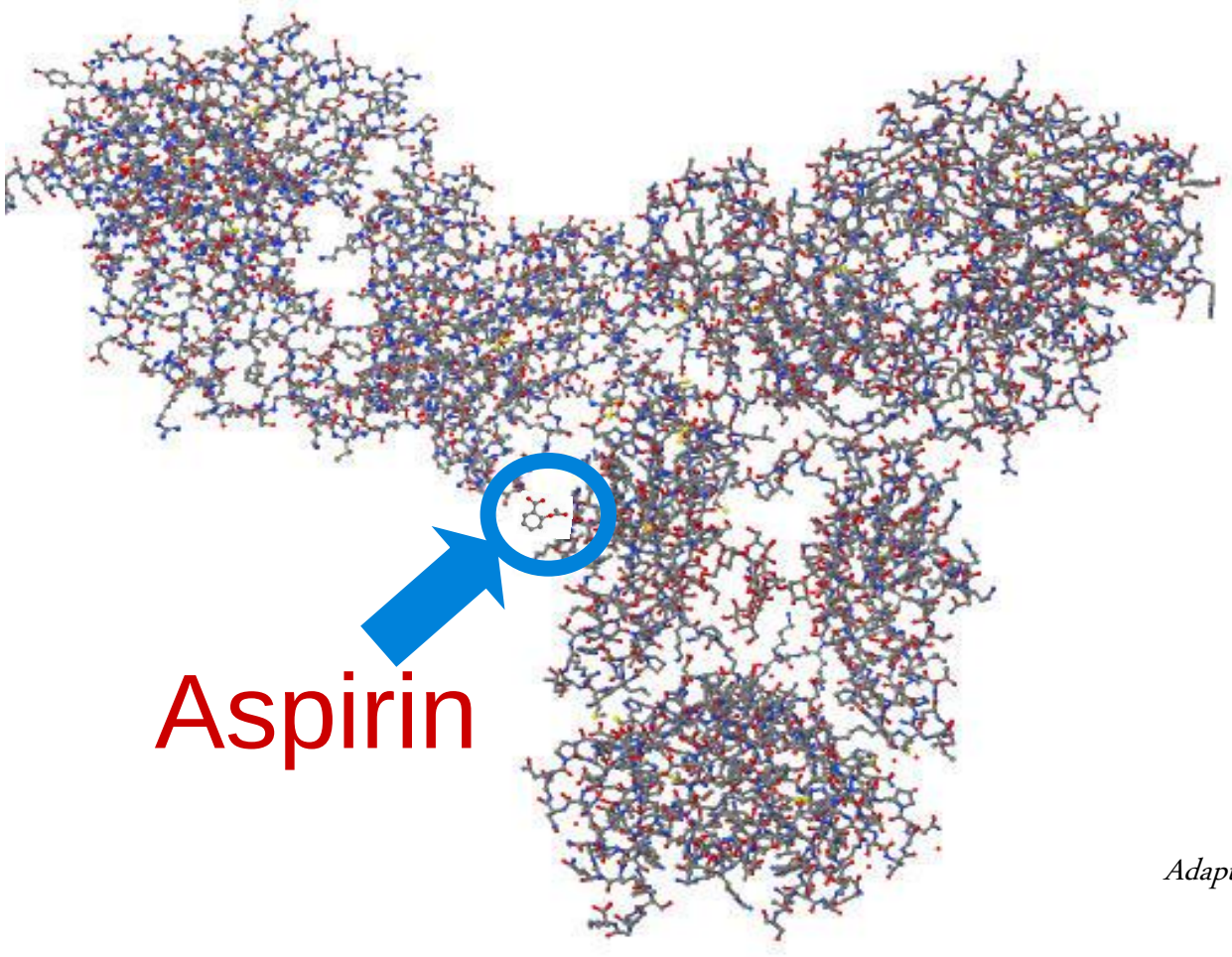
- Extrapolation of indications requires well-balanced assessments and might not be possible in many cases

FDA View on Extrapolation of Indications (Draft Guidance, February 2012)

Scientific Justifcation Should Address:

- The MOA (s) in each condition of use for which licensure is sought; this may include the following
  - The target/receptor(s) for each relevant activity/function of the product
  - The binding, dose/concentration response, and pattern of molecular signaling upon engagement of target/receptor(s)
  - The relationship between product structure and target/receptor interactions
  - The location and expression of the target/receptor(s)
- The PK and bio-distribution of the product in different patient populations; PD measures may provide important information on the MOA
- Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to off-target activities
- Any other factor that may affect the safety or effectiveness of the product in each condition of use and patient population for which licensure is sought

Monoclonal Antibody



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Summary

- Monoclonal Antibodies are very complex and identical copies using a different manufacturing process are impossible
- Biosimilar regulations are important to ensure safety of patients
  - Immunogenicity must be evaluated with any biologic
- Appropriate clinical studies must be conducted to evaluate biosimilars
- Extrapolation of clinical data is possible if justified based on a well understood mechanism of action of the therapeutic
- Pharmacovigilance is an important aspect of the safety evaluation of biologic products

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