Evaluation and requirements of the Common technical data CTDs for the Biosimilar drugs

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Agenzia Italiana del Farmaco

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Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

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Biologicals: Type of products

Macromolecules

Protein, polysaccharide extracted from body fluids or tissues of human or animal origin: Plasma-derived products, Urine-derived products (FSH, HCG....) ,Tissue- derived (heparin) ;

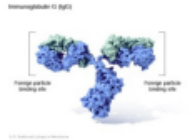
Recombinant proteins, including monoclonal antibodies

Vaccine

(live or inactivated)

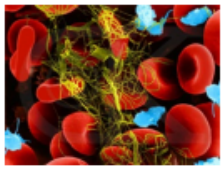
Types of Biological Products

Blood Derivatives

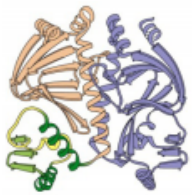


Whole Blood

Blood Components

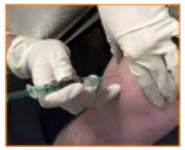


Proteins

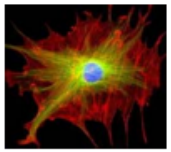


Human Tissues

Vaccines (preventive *and* therapeutic)



Allergenic Extracts



Cellular & Gene Therapies

Xenotransplantation Products

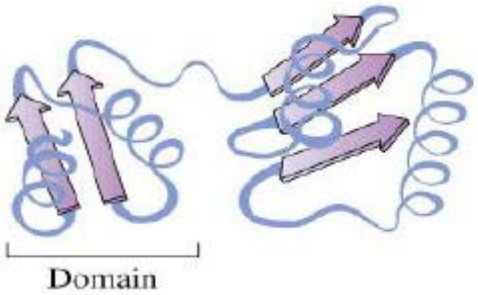
Complex structure

(a) Primary structure

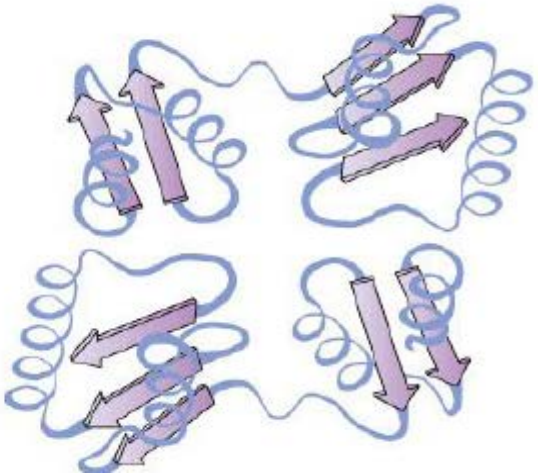
–Ala–Glu–Val–Thr–Asp–Pro–Gly–

(b) Secondary structure

(c) Tertiary structure



(d) Quaternary structure



“One process” – “One Product” paradigm

Fluctuation in the manufacturing process (pH, temperature, culture media)

Changes in the manufacturing process

Batch microheterogeneity

Batch variability

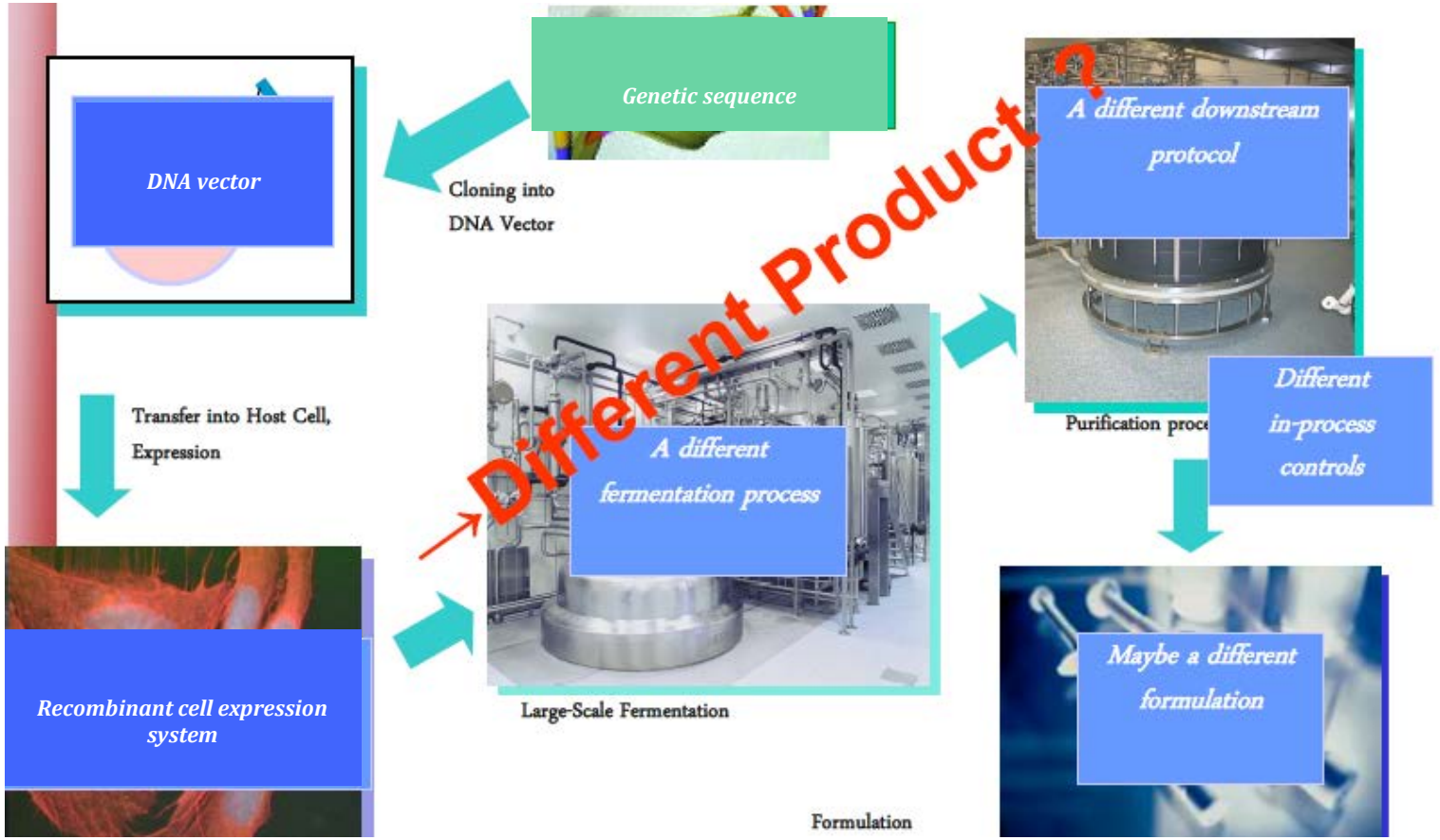
Batch inconsistency

“New product” after progressive drift?

Manufacturing process contributes to the product profile

Small changes may have high impact on Q/S/E

Biological Manufacturing Process



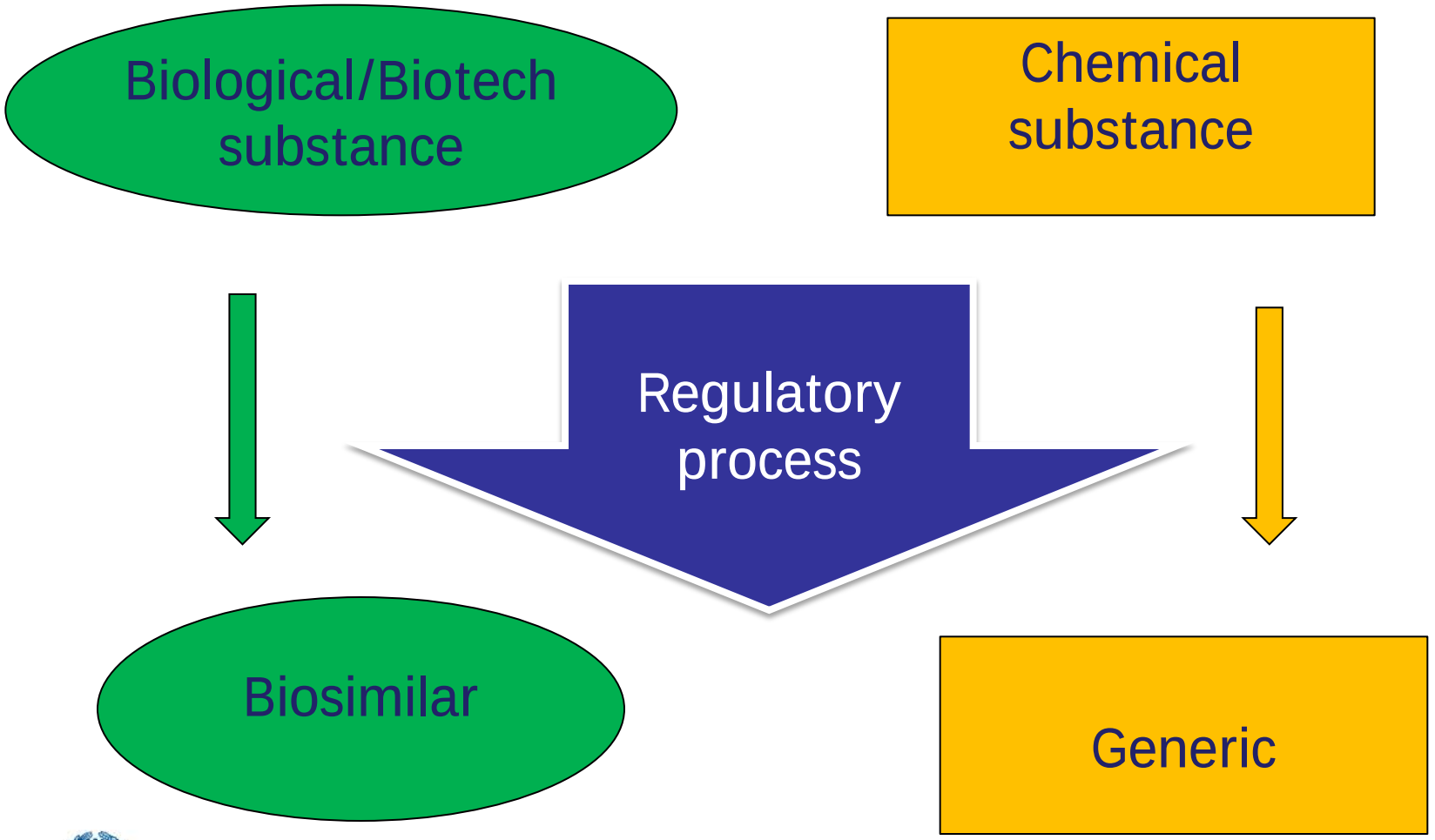
Biosimilars are similar, not identical, to original biotech products

Biosimilars are similar.....

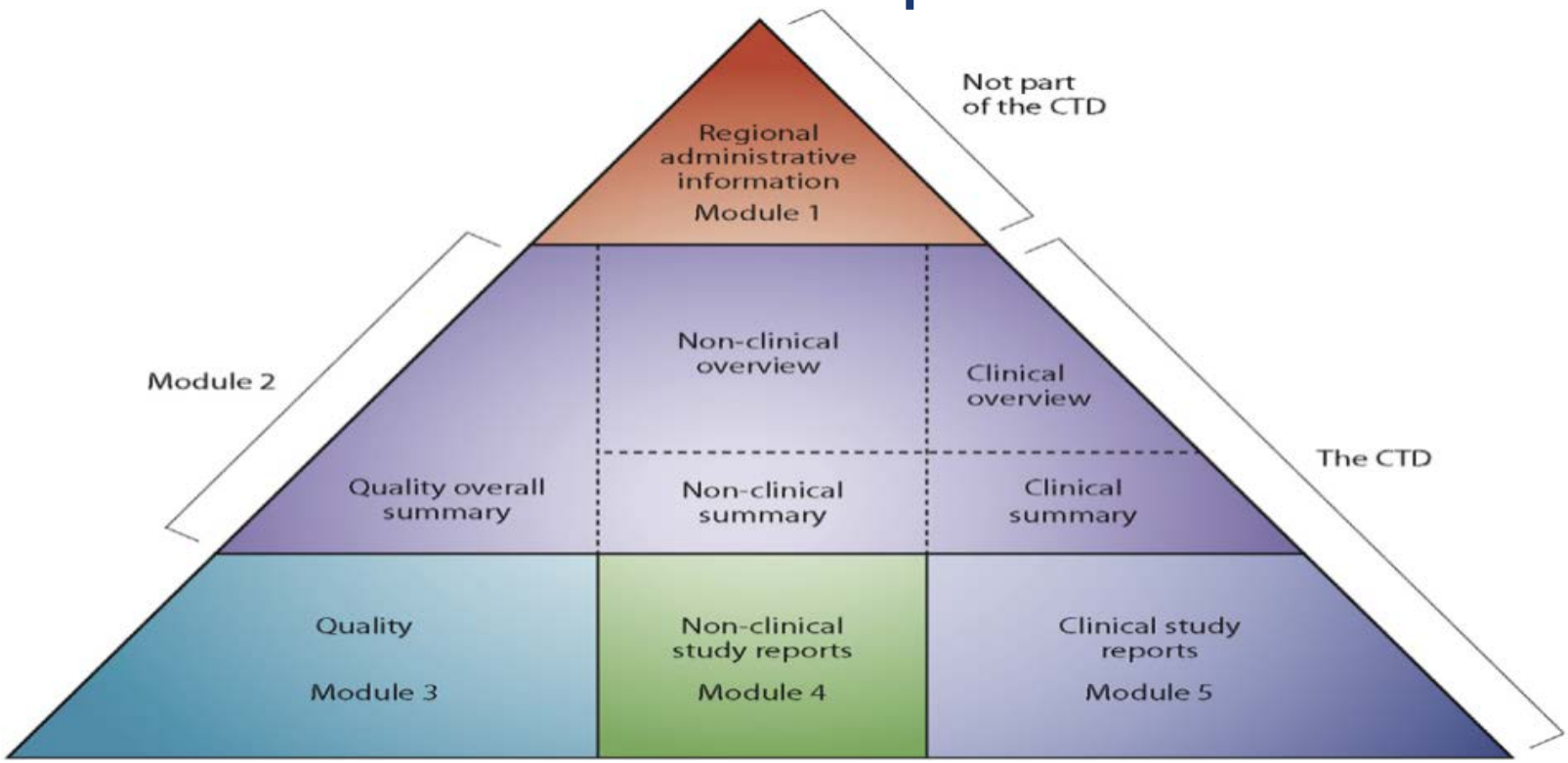
....Not Identical

Different cell lines
Different process

Small differences in substrate and manufacturing process may affect patient safety and clinical efficacy of the product


Biological/Biotech substance
Chemical substance
Regulatory process
Biosimilar
Generic

Documentation for a marketing authorization of a medicinal product

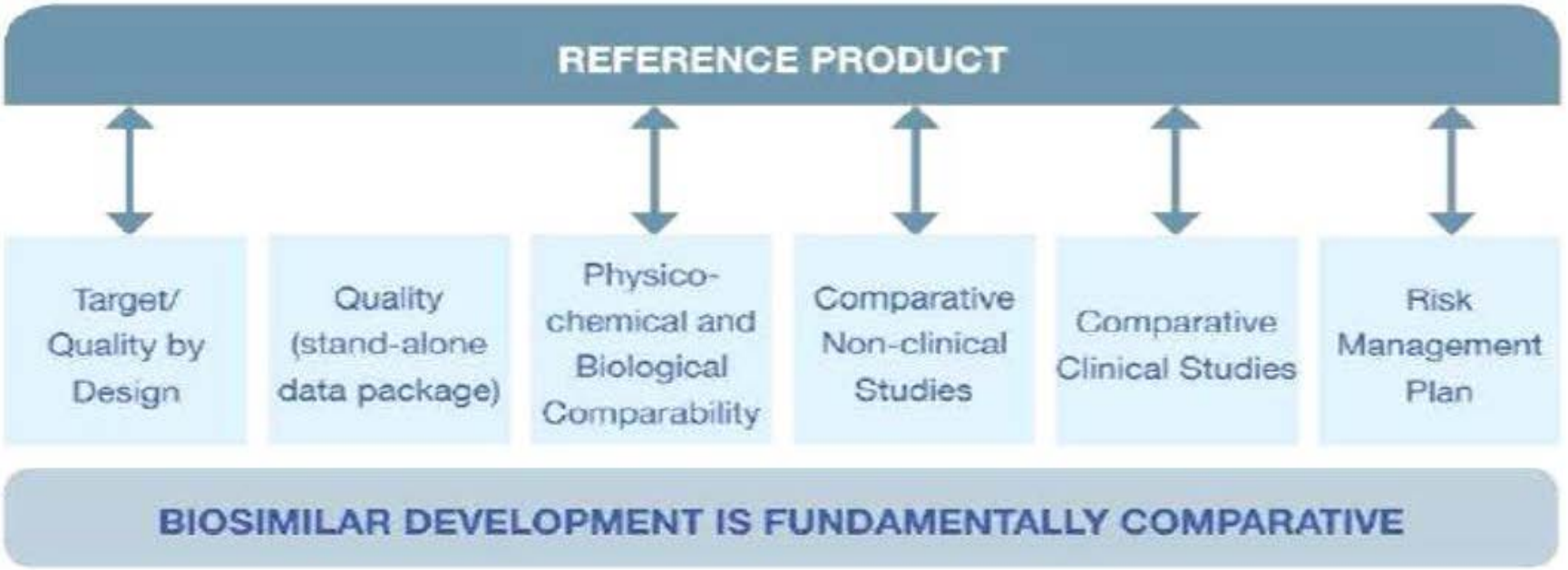


Stepwise approach starting with characterization and evaluation of quality attributes followed by non-clinical and clinical studies: PK, PD, clinical E and S trial(s).

Comprehensive characterization and comparison at the quality level are the basis for possible data reduction in the non-clinical and clinical development.

Differences should always be explained and justified and may lead to the requirement of additional data (*e.g.* safety data).

Authorization process for a biosimilar



CTD	Generic drug	Biosimilar
Module 1. Regional Administrative Information	Complete	Complete
Module 2. Overview of the modules 3,4 and 5	Complete	Complete
Module 3. Quality	Complete	Complete + Comparability exercise
Module 4. Non- Clinical study reports	Omitted / Bibliographic references	Results of pre-clinical studies + Comparability exercise
Module 5. Clinical study reports	Bioequivalence studies/biowaver	Results of clinical trials+ Comparability exercise

Biosimilar

Same posology and route of administration

Improving efficacy is out of the scope

Advantage in safety should be addressed (biobetter)

Worst case:	Best case:
Difficult to characterize by analytical techniques	Highly purified products
Narrow therapeutic index	Well characterized by analytical techniques
Uncertainty of MoA	Wide therapeutic index
	Wide clinical experience available

Applicant for a biosimilar product is responsible to provide the necessary evidence to support the biosimilarity.

Applicant should be able to demonstrate a full understanding of their products, consistent and robust manufacture of their products, and submit a full quality dossier that includes a complete characterization.

The ability for the biosimilar product to be authorized based on reduced non-clinical and clinical data depends on proof of its similarity through the comparability exercise.

Glossary

Comparability exercise: Head-to-head comparison of a biological product with a licensed originator product with the goal to establish similarity in quality, safety, and efficacy. Products should be compared in the same study using the same procedures.

Originator product: a medicine which has been licensed by the national regulatory authorities on the basis of a full registration dossier.

Glossary

Reference biotherapeutic product: is used as the comparator for head-to-head comparability studies with the similar biotherapeutic product in order to show similarity in terms of quality, safety and efficacy. Marketed for a suitable duration of time and sale volumes.

Similar biotherapeutic product (SBP): a biological product which is similar in terms of quality, safety and efficacy to an already licensed reference biological product.

Choice of reference product

With the aim of facilitating the global development of biosimilars and to avoid unnecessary repetition of clinical trials.

Choice of Reference Product: A single medicinal product authorised by the NCA

Coherent data and conclusion through the comparability exercise (quality, non clinical and clinical)

It may be possible to compare the biosimilar in certain clinical studies and in *in vivo* non-clinical studies (where needed) with a non-nationally authorised which will need to be authorised by a regulatory authority with similar scientific and regulatory standards as ICH.

Bridging data and information

Stepwise approach

Starting from physicochemical and biological characterisation

Extent and nature of non-clinical *in vivo* studies and clinical studies depending on evidence obtained in previous steps

Studies should detect differences (design, conduct, endpoints and/or population)

Quality

Manufacturing process: GMP

Characterization: knowledge of the analytical limitations of each technique

Physicochemical Properties

Biological Activity: confirming that a significant functional difference does not exist

Impurities: identified, quantified by state-of-the-art technology

Specifications

To verify the routine quality.

Defined acceptance limits for each test parameter.

Validated analytical methods.

To capture and control important product quality attributes.

Based upon the manufacturer's experience, experimental results.

Sufficient lots of SBP should be employed in setting specifications.

Can be different between the Reference and the Biosimilar.

Pharmacopoeial monographs may only provide a minimum set of requirements.

Stability studies

Measure how a pharmaceutical product maintains its quality attributes over time.

Carried out under various stress conditions (e.g. temperature, light, humidity, mechanical agitation).

Accelerated stability studies: can reveal otherwise-hidden properties and the degradation pathways of product.

Additional controls should be employed in the manufacturing process and during shipping and storage.

Practical Considerations on the Quality comparability approach

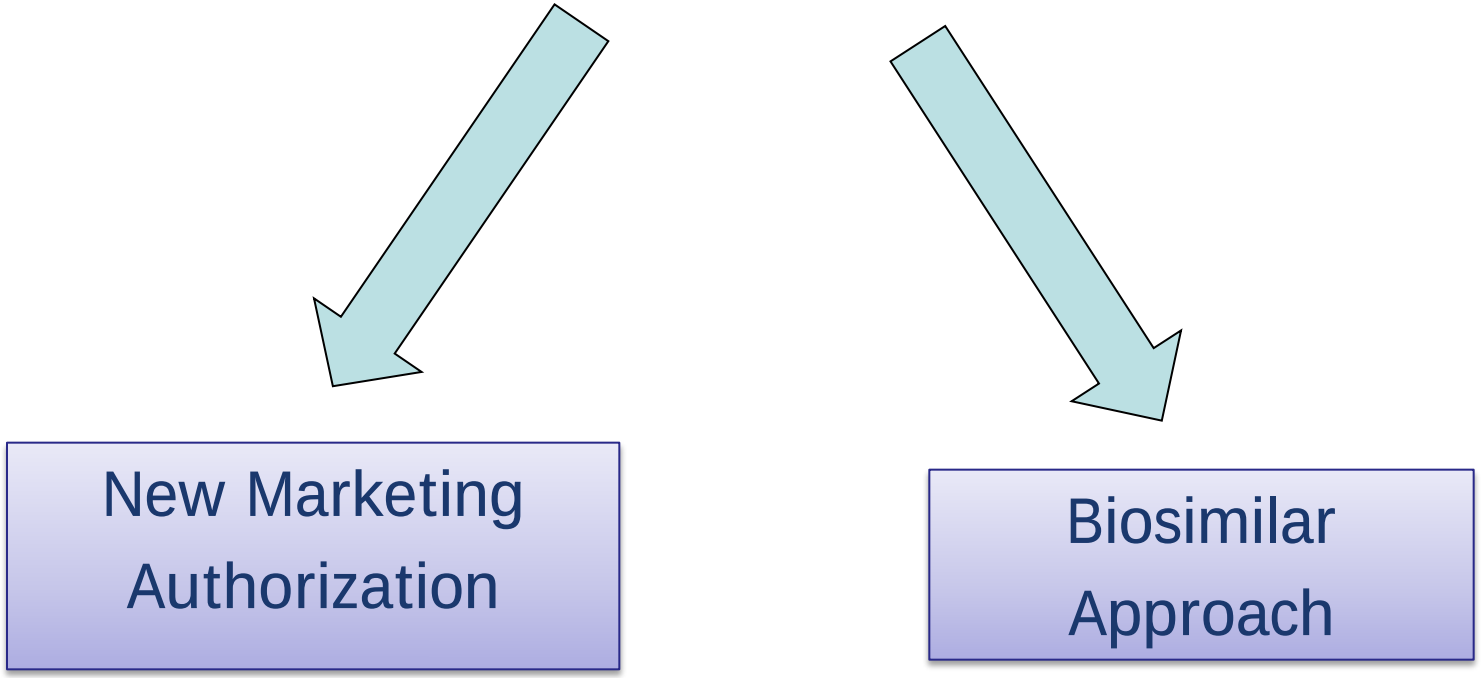
Applicants for biosimilars do not have access to confidential details of the manufacturing process of the Reference product.

The manufacturing process will be different.

The comparability exercise will usually be carried out using commercial drug (the final dosage form) containing the drug substance(s) formulated with excipients. Interference with analytical methods should be verified.

If the drug substance needs to be purified from a formulated reference drug product the product should be tested with and without manipulation.

Marketing Authorization: options



Biotechnological/biological products subject to changes in their manufacturing process

Scaling up

Transfer to alternative manufacturing sites

Manufacturing process

Methods of control

Change in the starting material and supply chain.

Comparability exercise: product attributes within the variability prior to change.

The “biosimilarity” question

How much “similarity” do we need?

EDITORIAL

mAbs 3:2, 107-110; March/April 2011; © 2011 Landes Biosciences

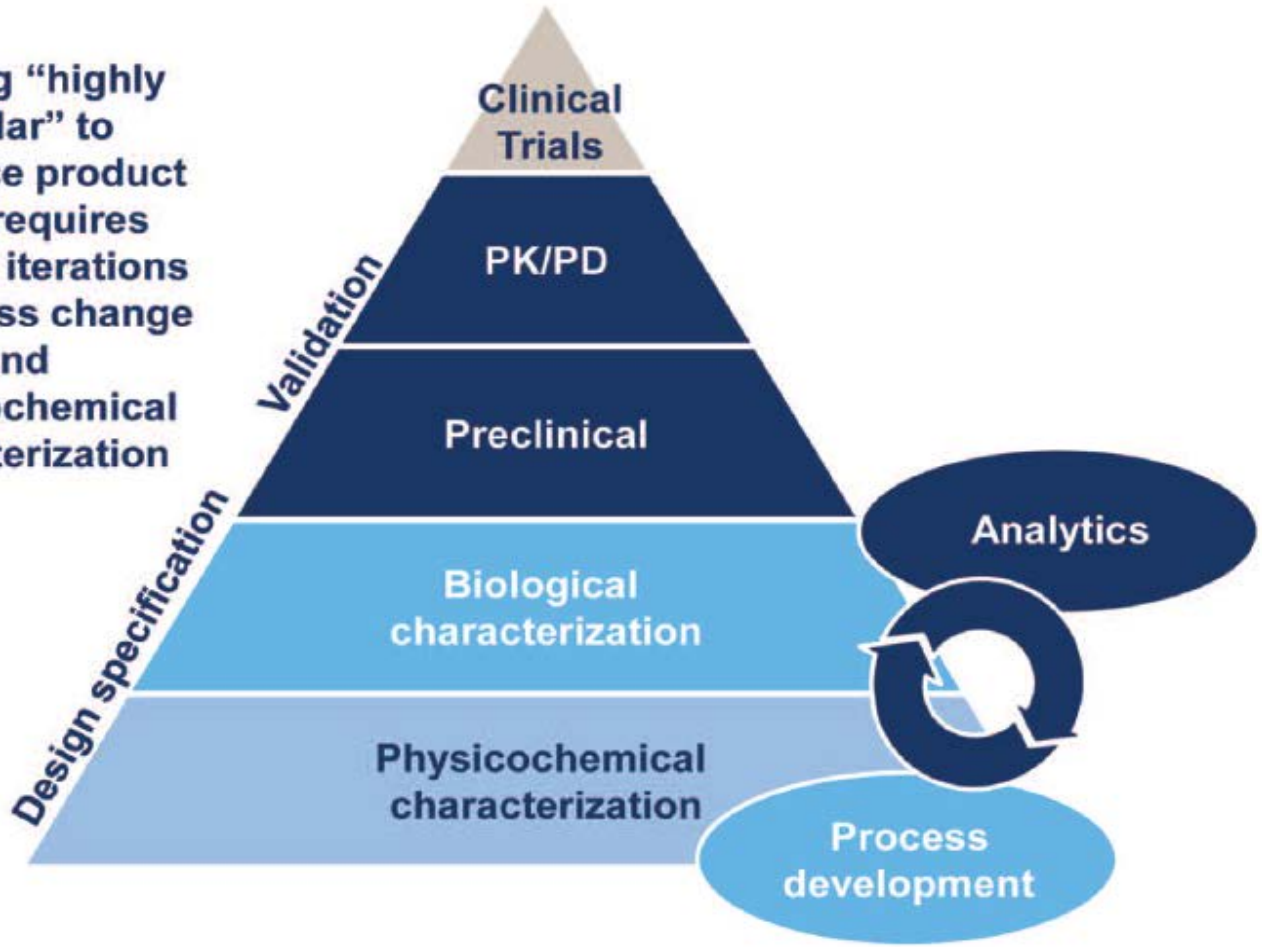
Biosimilar, biobetter and next generation therapeutic antibodies

Alain Beck

Can a biosimilar product be “better” than the originator?

“Bio-Better”

Proving "highly similar" to reference product often requires multiple iterations of process change and physicochemical characterization



Non-Clinical

To design an appropriate non-clinical study program, a clear understanding of the MOA of reference product characteristics is required.

Comparative studies.

In vitro (i.er. Biological assays, binding assays, enzyme kinetics).

In vivo in animal model of the disease to evaluate functional effects on pharmacodynamic marker or efficacy measures.

Toxicological studies: scope and extent depend on information about the reference product and the differences with the biosimilar.

Discussion of the limitation of the assays.

Clinical

Nature and scope of clinical studies depend on:

Residual uncertainty about biosimilarity after quality and non-clinical studies;

Frequency and severity of safety risks and effectiveness considerations (i.e. poor relationship between pharmacologic effects and effectiveness);

PK and PD studies: justification of the selection of the human study population (patients vs. healty subjects), the relevance of the PD measures to clinical outcomes, and the sensitivity to allow for the detection of differences between the reference vs. the biosimilar.

Additional comparative clinical studies (if needed)

Additional comparative clinical studies

Factor that may influence the type and extent:

Outcome of quality, non-clinical, PK/PD comparability studies.

Extent of clinical experience with the reference product and the therapeutic class.

Safety and risk benefit profile.

Appropriate endpoints and biomarkers for safety and effectiveness.

Worldwide clinical experience with the product.

Immunogenicity assessment

Analysis of risk factors:
Previous experience of the product/product class
Physicochemical and structural aspects
Route and/or the mode of administration
Patient - and disease - related factors

The overall immugenicity assessment should consider the nature of the immune response (anaphylaxis, neutralizing antibodies), the clinical relevance and severity of consequences (loss of efficacy and other adverse events), the incidence of immune responses, and the population being studied.

Extrapolation of efficacy and safety from one therapeutic indication to another

When biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable, but needs to be scientifically justified. In case it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication, additional data will be required. Extrapolation should be considered in the light of the totality of data, i.e. quality, non-clinical and clinical data.

Extrapolation of efficacy and safety from one therapeutic indication to another

Additional data are required in certain situations, such as:
1. the active substance of the reference product interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indications;
2. the active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications;
3. the studied therapeutic indication is not relevant for the others in terms of efficacy or safety, i.e. is not sensitive for differences in all relevant aspects of efficacy and safety.

Population size and number of trials for assessing biosimilarity

Active substance	Product	Company	Number of subjects in PK/PD studies (P: patients, V: volunteers)	Number of PK/PD studies	Number of patients in phase III studies	Number of phase III studies	Compared with reference product in phase III studies?
Epoetin alfa/zeta	Silapo/Retacrit	Stada Arzneimittel AG/ Hospira UK Limited	72 (V)	2	1272	3	Yes
	Epoetin Alfa Hexal/Abseamed/ Binocrit	Hexal/Medice Arzneimittel Puetter/Sandoz	234 (V)	5	592	2	Yes
Filgrastim	Zarzio/Filgrastim Hexal	Sandoz/Hexal	146 (V)	4	170	1	No
	Tevagrastim/ Ratiograstim/ Biograstim	Teva Generics/ Ratiopharm/ ABZ-Pharma	200 (V)	2	677	3	Yes
	Nivestim	Hospira UK Ltd	92 (V)	2	279	1	Yes
	Grastofil/Accofil	Apotex Europe BV/Accord Healthcare	215 (V)	4	120	1	No
Follitropin alfa	Ovaleap	Teva Pharma	76 (V)	2	299	1	Yes
	Bemfola	Finox Biotech	24 (V)	1	273	1	Yes
Insulin glargine	Abasaglar	Eli Lily	211, 20 (V, P)	5	1295	2	Yes
Somatropin	Omnitrope	Sandoz	61 (V)	3	140	2	Yes
Etanercept	Benepali	Samsung Bioepis UK Limited	138 (V)	1	596	1	Yes
Infliximab	Remsima/ Inflectra	Celltrion Healthcare/ Hospira UK Limited	269 (P)	2	606	1	Yes
	Flixabi	Samsung Bioepis UK Limited	159 (V)	1	584	1	Yes

PD, pharmacodynamic; PK, pharmacokinetic. All information is taken from the EPARs [19–39]

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) •• ••–•• 1

SYSTEMATIC REVIEW

Clinical trials for authorized biosimilars in the European Union: a systematic review

Pharmacovigilance

Rare but potentially serious safety risks may not be detected during preapproval studies because the size of the study population.

Routine Pharmacovigilance surveillance

Post marketing studies

The RMP of the biosimilar should take into account identified and potential risks associated with the use of the reference product.

Risk minimization Measures
Additional Monitoring

Benefit-Risk Balance

Proactive and innovative approach: peer-review of literature, use of social media tools, PROMs

VigiBase: the WHO Global Individual Case Safety Reporting (ICSR) System

Spontaneus reporting System
ICSR provided by more than 80 Countries
Pooling of national data into global database

Analyses: combination of authomated screening, further filtering by triage, and clinical assessment by pannel of international experts.

Disanvantages:
Under reporting and missing data
Heterogeneity of timing, completeness and quality of report

Advantages:
Continuous data collection
Low cost
Broad population coverage
Opportunity to make country comparison and to identify and analyse differences

Pharmaceutical development and access

Critical issues:
Pricing policy
Intellectual property rights
Regulatory environment
Scientific and technology capacities

Consequences on the global system of research, manufacturing, distribution and use of medicines.

Medicines Regulatory Agencies

Protect the health and safety of the population ensuring the safety, quality, and efficacy of medicines.

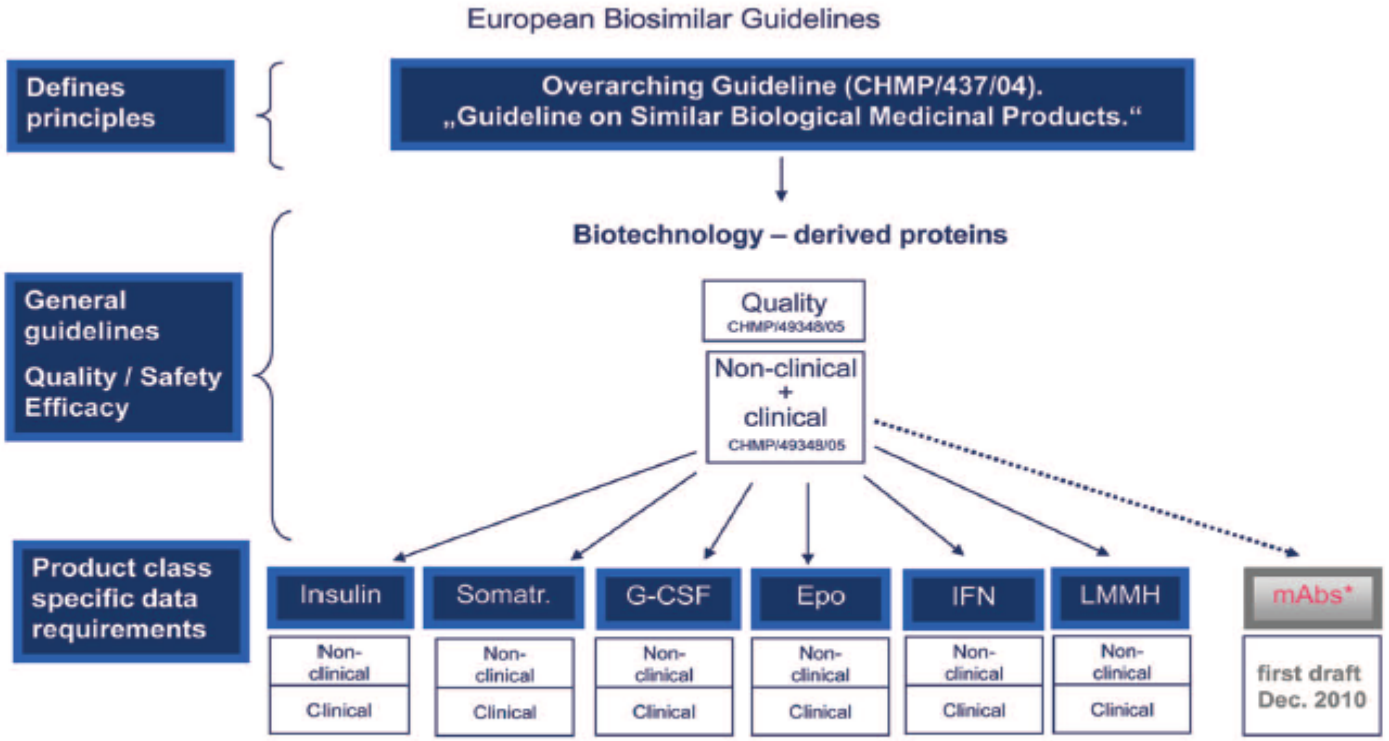


Figure 1. European biosimilar guidelines. The EMA began with an overarching guideline on biosimilars and then general guidelines, before issuing product class specific data requirements. The EU Guidelines that have been finalized are indicated in blue. A draft guideline for mAbs is currently available for public comment.[25]

Global level

Roles for safety, quality, and efficacy of medicines.

Local level

intellectual property issues; interchangeability and substitution; labelling and prescribing information.

Label and prescribing information

Record of batch information for traceability porpouse
Indication of biomilarity in SPC for the biosimilar
Use of Non Proprietary Name of the Reference

Some Cases

Heparins

Mab

Insulin

Erithropoietin

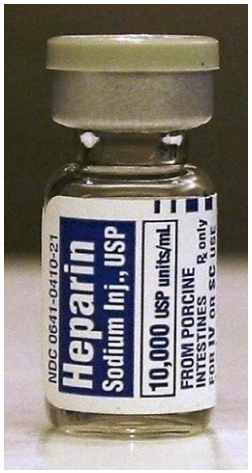
Somatropine

Biosimilar Heparin/LMWH

Physicochemical properties

Equivalence of source material and mode of depolymerization

Disaccharide building blocks, fragment mapping and sequence of oligosaccharide species



Manufacturing process

Biological and biochemical assays

In vivo pharmacodynamic profile

Characterisation of the interaction for PF4

Biosimilar Heparin/LMWH

Acceptance criteria should be established prospectively

No new compositional species (near the LOD) should be present and all constitutive component species of the LMWH present in the reference product are also present in the test product.

Waiving of certain non-clinical and clinical studies provided that similar efficacy of the biosimilar and the reference product can be convincingly deduced from the biosimilar step-wise approach.

Discussion of any quality aspects that might have implications on pharmacology of the product candidate, including safety implications of excipients and considerations on immunogenicity

Clinical development of biosimilar LMWHs

Pharmacodynamic activities (anti FXa and anti-FIIa activity), should be compared between the biosimilar and the reference LMWH, as well as the ratio of anti-FXa and anti-FIIa activity.

Pharmacodynamic properties should be investigated in a randomized, single-dose, two-way crossover study in healthy volunteers using subcutaneous administration.

If similar efficacy of the biosimilar from the comparison of physicochemical characteristics, biological activity/potency, and from comparison of their PD profiles, a dedicated efficacy trial may be waived. (EMEA/CHMP/BMWP/118264/2007 Rev. 1)

Some Cases

Heparins

Mab

Insulin

Erithropoietin

Somatropine

Monoclonal Antibodies

Rituximab:

2017 Ritemvia, Blitzima, Riximyo, Rixathon, Truxima, Rituzena highly similar to MabThera

Adalimumab:

2017 Amgenvita, Cyltezo, Imraldi highly similar to Humira

Infliximab:

2013-2016 Inflectra, Remsima, Flixabi highly similar to Remicade

Etanercept:

2016 Benepali, Erelzi highly similar to Enbrel

Some Cases

Heparins

Mab

Insulin

Erithropoietin

Somatropine

LANTUS (Originator) vs ABASAGLAR (Biosimilar)

Required the same therapeutic indication of the Originator.

MA of the Originator:
10 clinical studies on a total of 2106 subjects; pediatric studies conducted (261 subjects 2-18 of age).

vs

MA of the Biosimilar:
2 clinical studies on a total of 1295 subjects; no pediatric studies.

Some Cases

Heparins

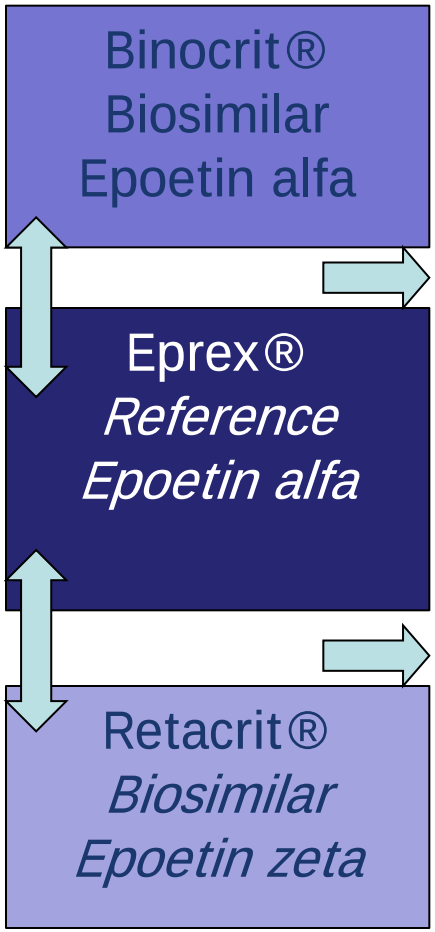
Mab

Insulin

Erithropoietin

Somatropine

rHuEPO Epoetin



Quality: Difference in glycosylation levels

- One randomized controlled trial involving 479 haemodialysis patients with renal anaemia
- Data from a study involving 114 cancer patients receiving chemotherapy were also submitted for approval but this study was not adequately powered to demonstrate therapeutic equivalence to the reference product
- Biosimilar epoetin alfa was approved for indications in cancer patients and patients planning to undergo surgery (for autologous blood transfusions) = Extrapolation

Difference in glycosylation profile and a different immunogenicity profile in dogs

- Two randomized clinical trials,a correction phase study and a maintenance phase study, involving 922 haemodialysis patients with renal anaemia.
- A study involving 261 cancer patients receiving chemotherapy, but this study was not designed to demonstrate therapeutic equivalence between products in this patient population.
- Approved for indications in renal anaemia, chemotherapy-induced anaemia, and for pre-donation of blood prior to surgery for autologous transfusion.

Some Cases

Heparins

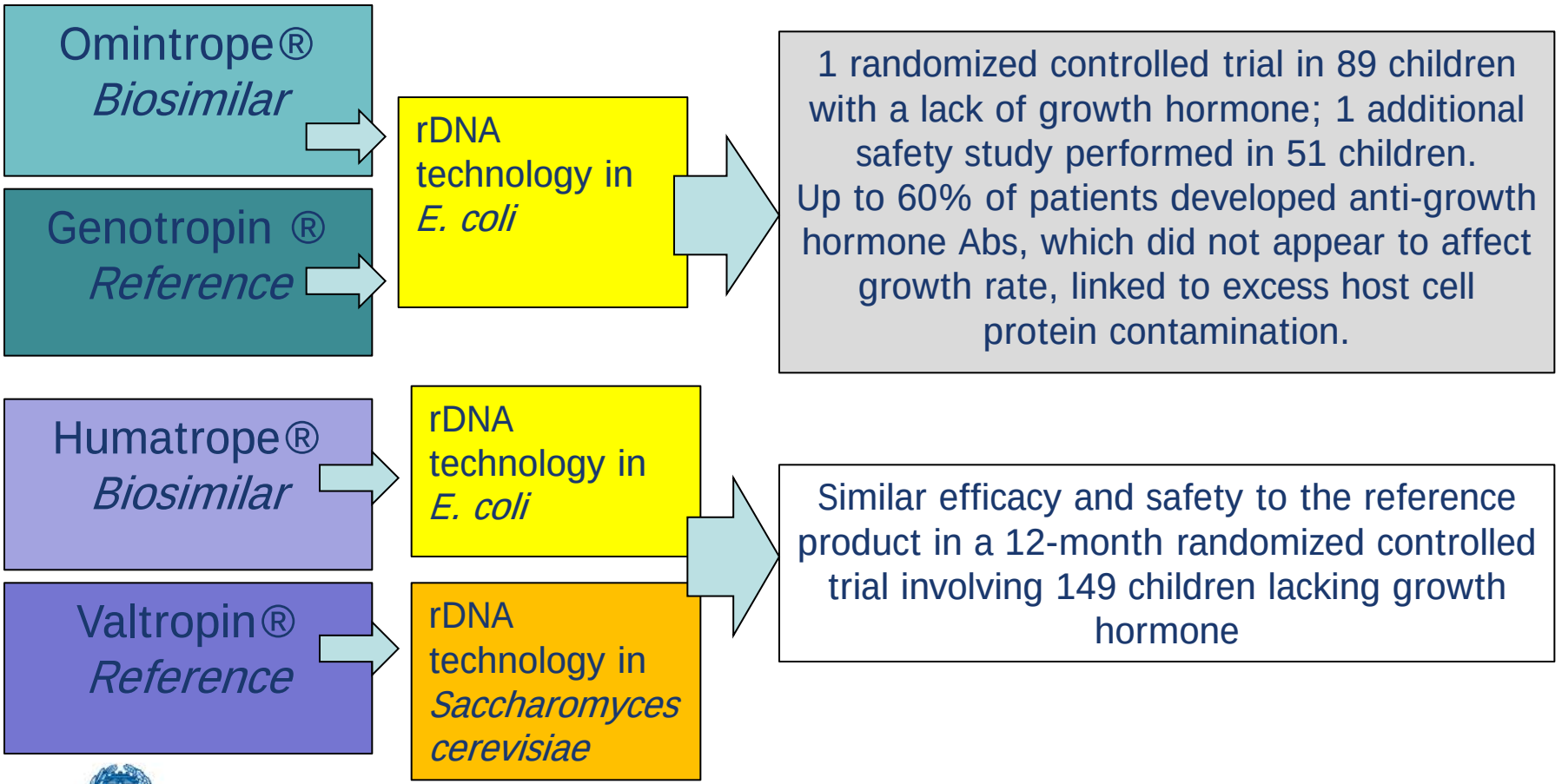
Mab

Insulin

Erithropoietin

Somatropine

Somatropine



Conclusion

There is a need to comprehensively test biosimilars during the production process and always in comparison with an appropriate reference product.

Although a variety of assays are available, they may not be adequate to reliably predict the safety and efficacy of a biosimilar product.

The validation and standardization of assays is crucial for future testing and regulation of biosimilars.

The regulatory approval of biosimilars requires the demonstration of pharmaceutical equivalence and pharmacokinetic bioequivalence much more than conventional generics.

Conclusion

In the post-PRCA era, the immunogenicity of recombinant therapeutic proteins has become a significant safety concern.

Ultimately, reduced clinical studies and post-authorization pharmacovigilance to monitor potential immunogenicity provide definitive evidence for product comparability with respect to safety and efficacy.

Manufacturing and clinical experience with the first biosimilar products are of great value.

Conclusion

Outstanding issues will need to be resolved

Substitution, naming and labelling.
Unique naming for all would facilitate prescribing, dispensing and pharmacovigilance.

Transparent label and information on relevant clinical data (i.e. EPAR), would help prescribers and other healthcare professionals to make informed treatment decisions.

Thank you for your attention!

CONTATTI

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