

Similaridade entre produtos biológicos: conceitos e tendências

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Biosimilar development

Cell Line Development & Master Cell Bank characterization



Upstream and downstream process development



Comparative evaluation of structural characteristics
and post-translational modifications



Comparative study of process- and product-related impurities



Comparative evaluation of functional properties



Strong evidence of biosimilarity *in vitro*



Non-clinical studies in non-human primates

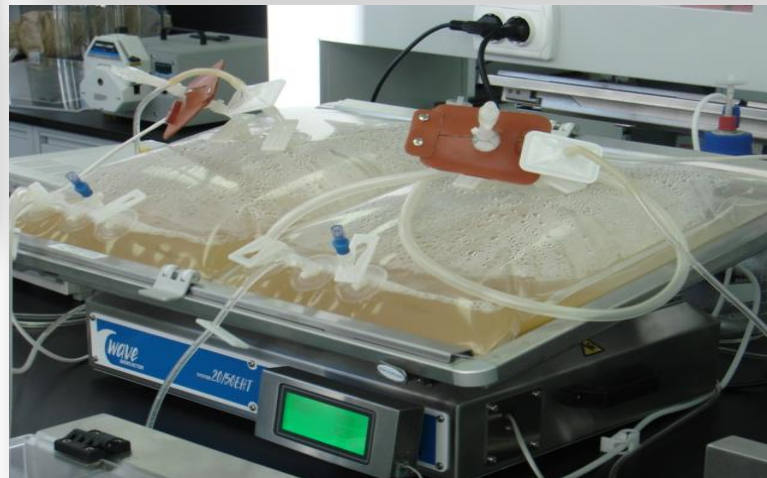


Comparable PK characteristics in a clinical study



Comparative efficacy, safety and immunogenicity clinical study

Single-use technology



BIOSIMILARS GLOBAL REGULATION

European Union



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



The EMA was the first agency to issue guidelines for the approval of biosimilars back in 2004. Since then, several biosimilars have become available in EU.

Directive 2001/83/EC

- Article 10(4): legal requirements

Regulation (EC) 726/2004

- Article 6: legal procedures



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General Guidelines (all biosimilars)

Specific Guidelines (individual biosimilars)

MAA Requirements (EU)

Quality data	<p>CMC standards equivalent to the reference product</p> <ul style="list-style-type: none">✓ Manufacturing process, control tests and standards✓ In-process control of the manufacturing✓ Data on analytical tests (molecular structure; potency and purity/impurity profile)
Pre-clinical data	<p>Determined on case-by-case</p> <ul style="list-style-type: none">✓ Abbreviated program of in vitro and in vivo tests.✓ May include animal testing.
Clinical data	<p>Studies in patients and healthy volunteers</p>
Pharmacovigilance	<p>Pharmacovigilance System and Risk Management Plan</p> <ul style="list-style-type: none">✓ Pharmacovigilance✓ Post marketing surveillance

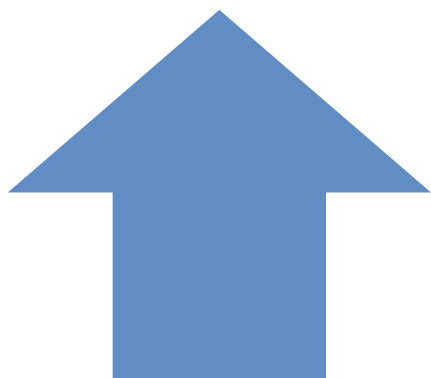
2009 Biologics Price Competition and Innovation (BPCI) Act, enacted under the 2010 Patient Protection and Affordable Care Act (ACA)

- First step in the development of a biosimilar regulatory process in the US
- Accelerated approval for biosimilars (deemed to be interchangeable with the reference biologic)

Interchangeability criteria



Biosimilar



Interchangeability

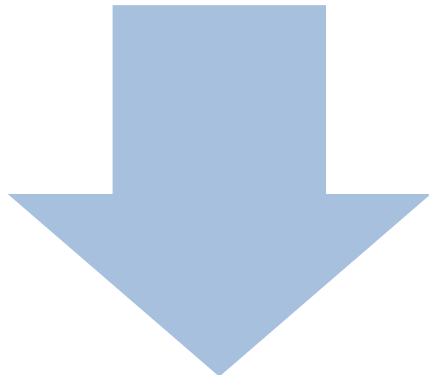
Safety, efficacy,
and potency

Same clinical
response

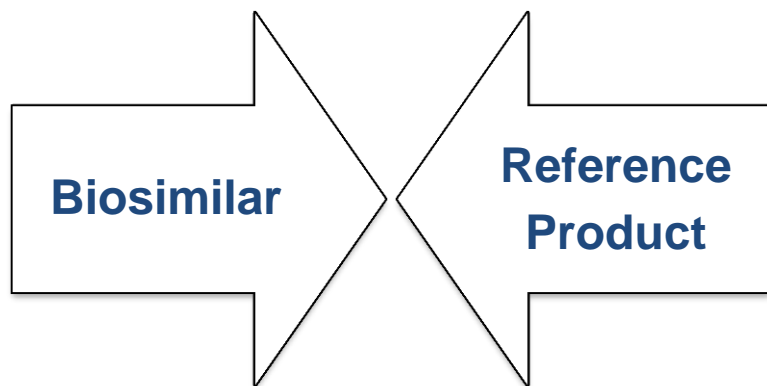
no significant
differences

Therapeutic
equivalence

Reference Product



FDA Approval Process



- Criteria:
 - Identical primary amino acid sequence
 - Extensive comparison of physicochemical and functional characteristics
 - Comparable quality, safety, and efficacy in head-to-head pre-clinical and clinical trials

FDA Approval Process

Pre-registration activities

Biosimilar vs.
Reference in key
indications

PK / PD
comparability

In vivo, in vitro
assays (functional
biosimilarity in
animal models)

Comparability of
protein structure and
quality attributes

Clinical
Studies
(Phase III)

Clinical Studies
(Phase I)

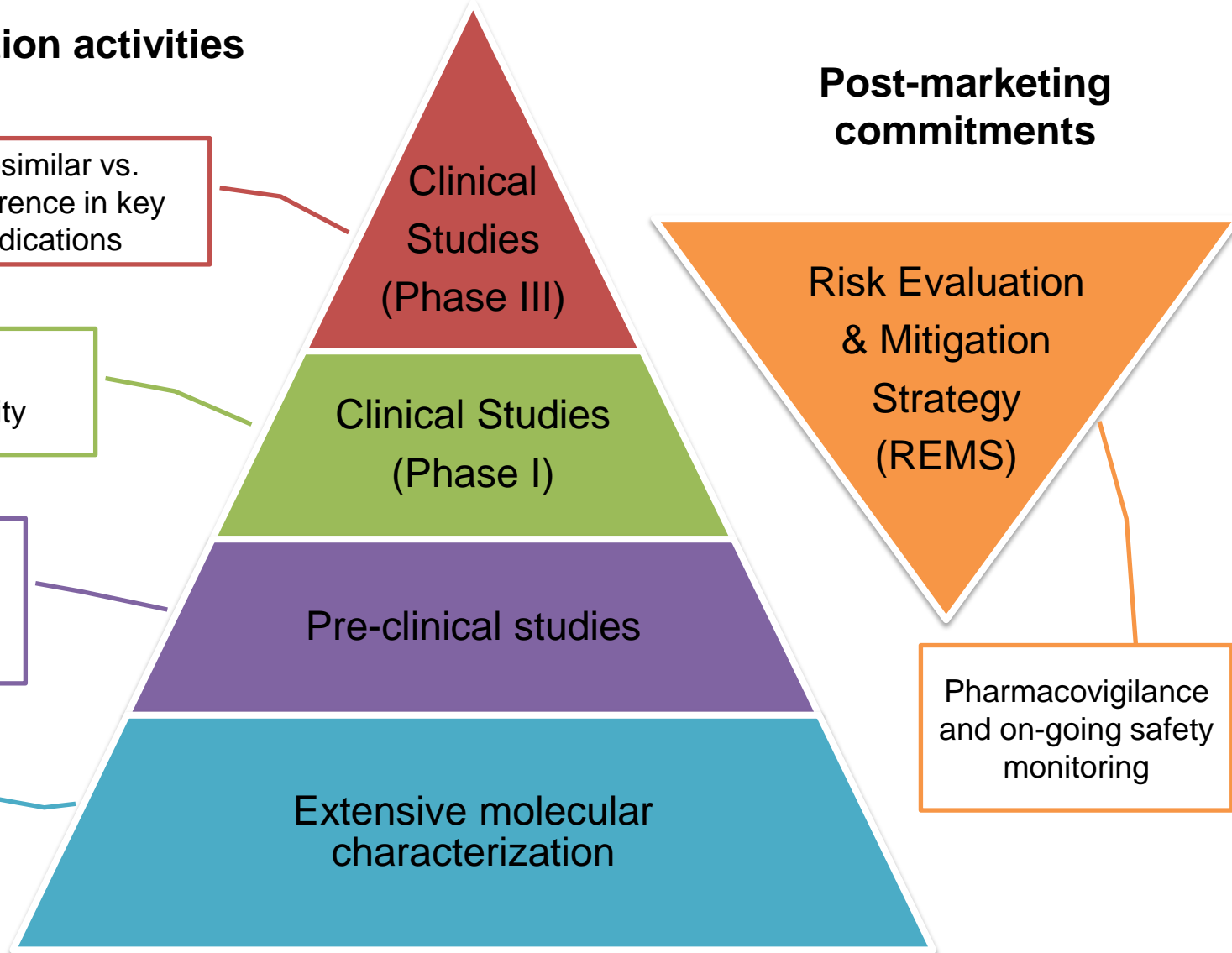
Pre-clinical studies

Extensive molecular
characterization

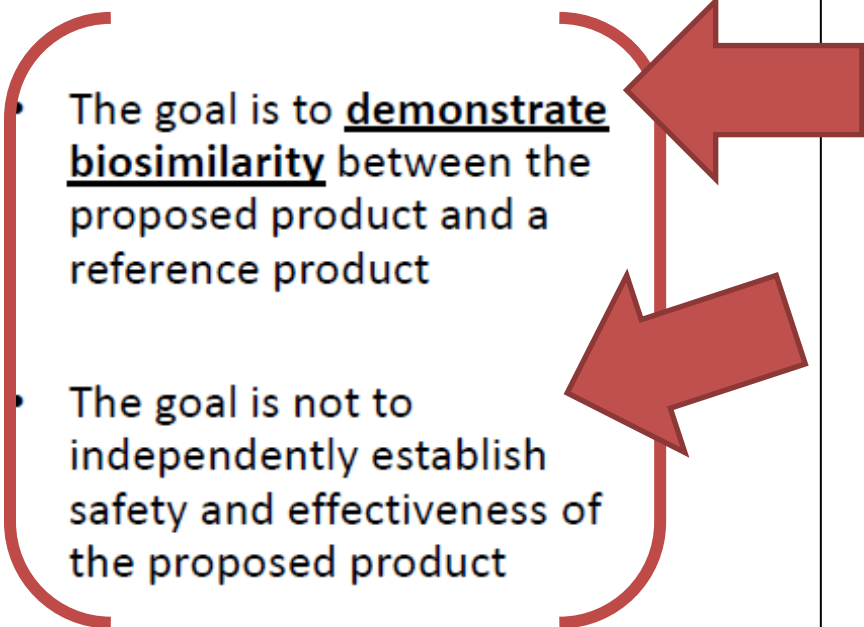
Post-marketing commitments

Risk Evaluation
& Mitigation
Strategy
(REMS)

Pharmacovigilance
and on-going safety
monitoring



Key Concept #1: Goals of “Stand-alone” and Biosimilar Development are different

- The goal of “stand-alone” development is to demonstrate that the proposed product is safe and efficacious
 - Drug development starts with preclinical research, moves to Phase 1, 2 and culminates in Phase 3 “pivotal” trials to show safety and efficacy
- The goal is to demonstrate biosimilarity between the proposed product and a reference product
 - The goal is not to independently establish safety and effectiveness of the proposed product
- 

What does this difference mean from a development perspective?

Plan the Program

- Apply a step-wise approach to data generation and the evaluation of residual uncertainty*

Analytical Studies



Animal Studies



Clinical PK/PD Studies



Clinical Immunogenicity Assessment



(Additional Clinical Studies)



* The list is not intended to imply that all types of data described here are necessary for any given biosimilar development program. FDA may determine, in its discretion, that certain studies are unnecessary in a 351(k) application.



**World Health
Organization**

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

WHO Guidelines on the Evaluation of Similar Biotherapeutic Products (SBPs), 2009

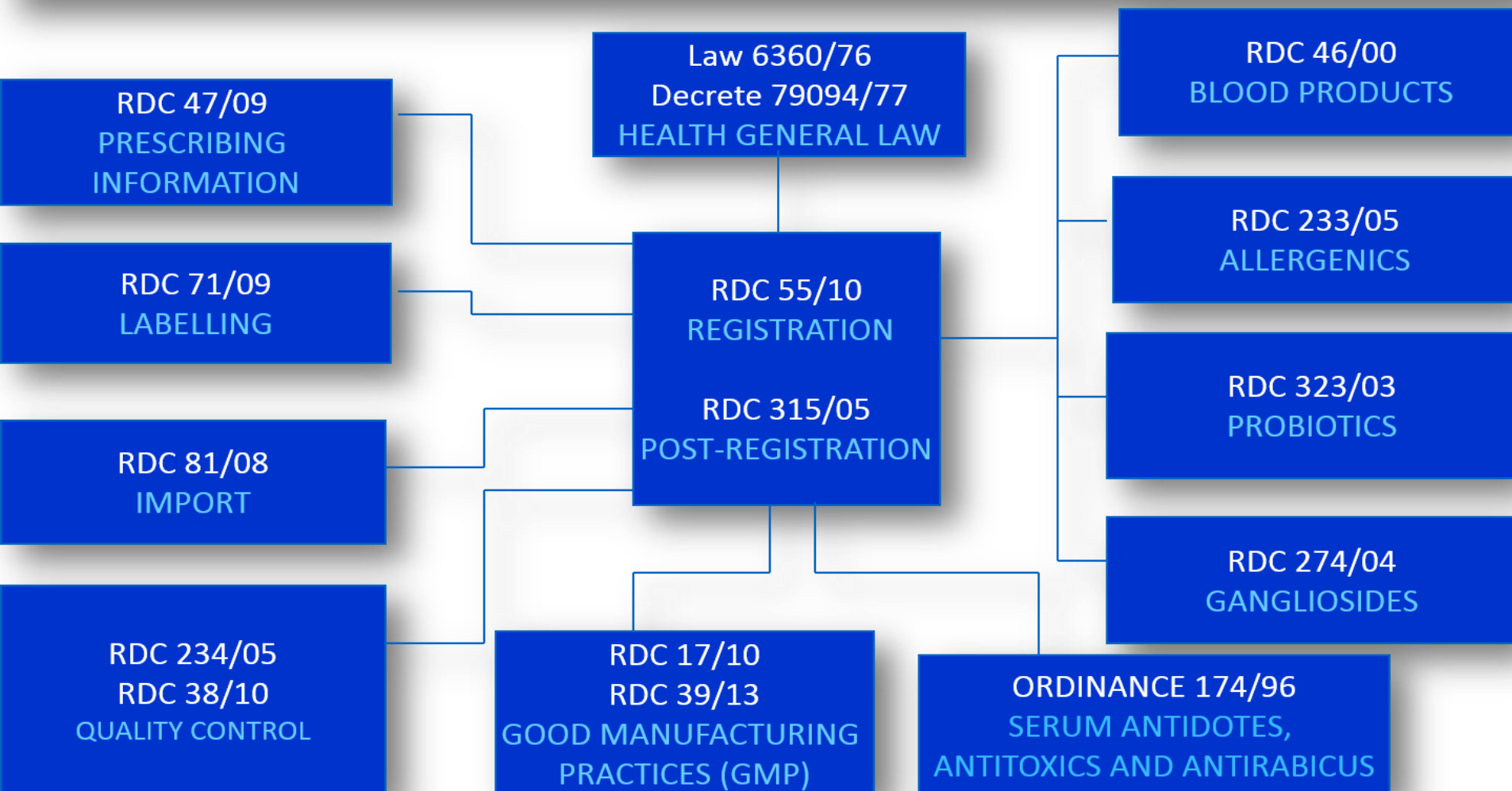
□ Main reference for LATAM authorities

Topics covered (Chapters):

5. Scientific considerations and concept for licensing SBPs
6. Key principles for the licensing of SBPs
13. Roles and responsibilities of National Regulatory Agencies
(NRAs)

BRAZIL (ANVISA)

Regulatory Framework For The Registration Of Biological Products



Regulatory Pathways For The Register Of Biological Products

Complete Dossier

Individual Development

Development through comparability

Complete filling dossier
(without data reduction)

Complete dossier
Non-inferiority studies (phase
III-demonstration of
therapeutic activity and safety)

Complete quality dossier
- Comparability Exercise (Essay)
- Reduced non-clinical data
- Comparative clinical data

New Biological Product

Biological Product (not new)

Biological Product (not new)



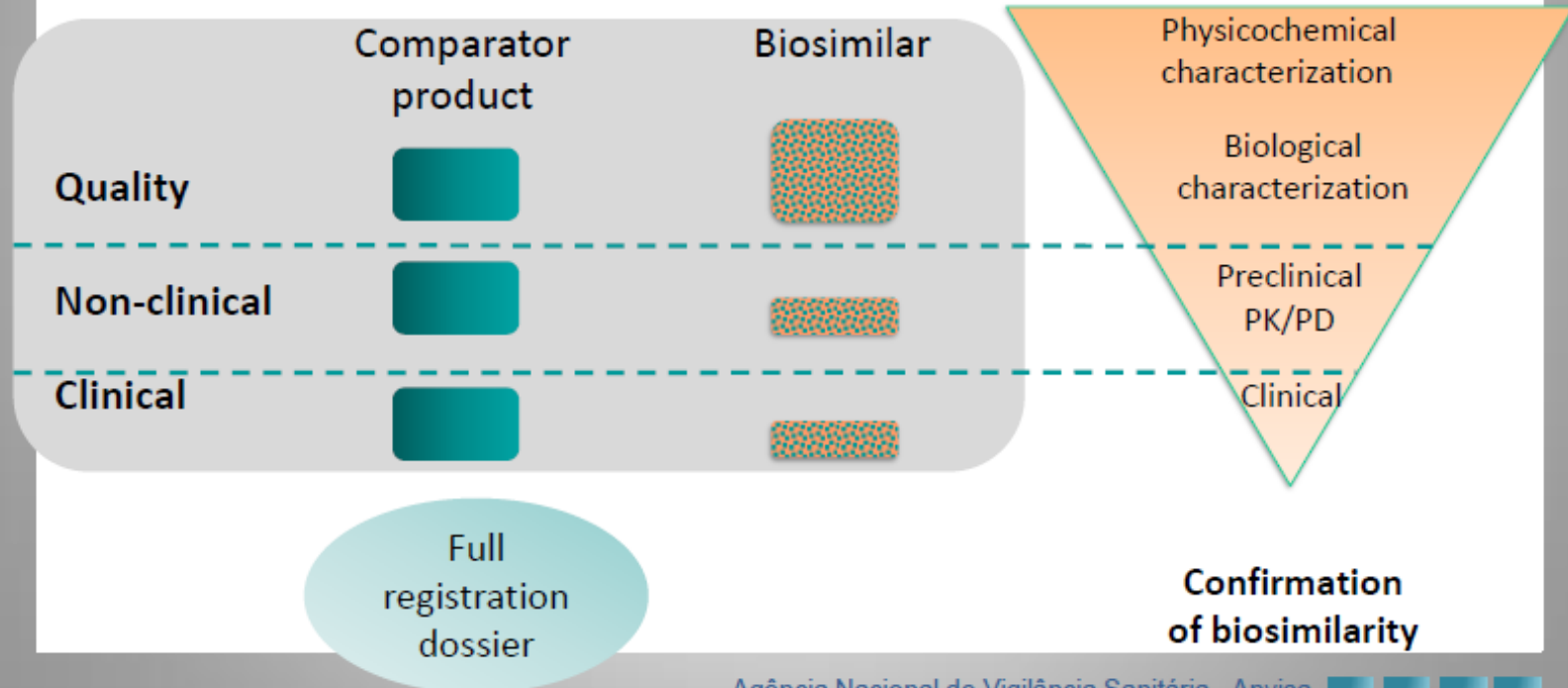
Registro de Produtos Biológicos

RDC 55/2010

Via de desenvolvimento por comparabilidade – Via do Biossimilar

Head-to-head comparison

Comparability exercise:
Quality, Efficacy and Safety.



Agência Nacional de Vigilância Sanitária - Anvisa

ICH Q6B guidelines

(1) Impurities

(endotoxines, leached protein A, host cell protein, host cell DNA and viruses)

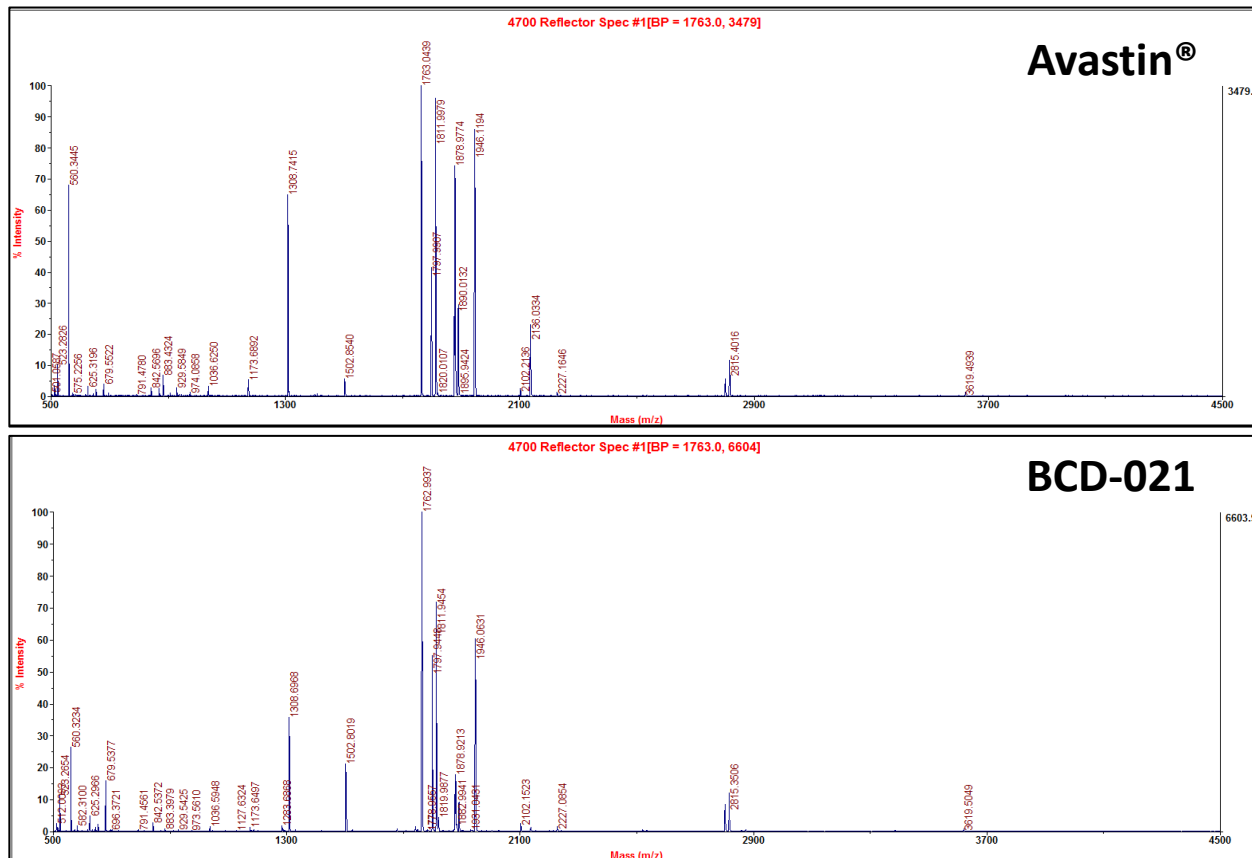
(2) Purity

(3) Physicochemical properties and structural

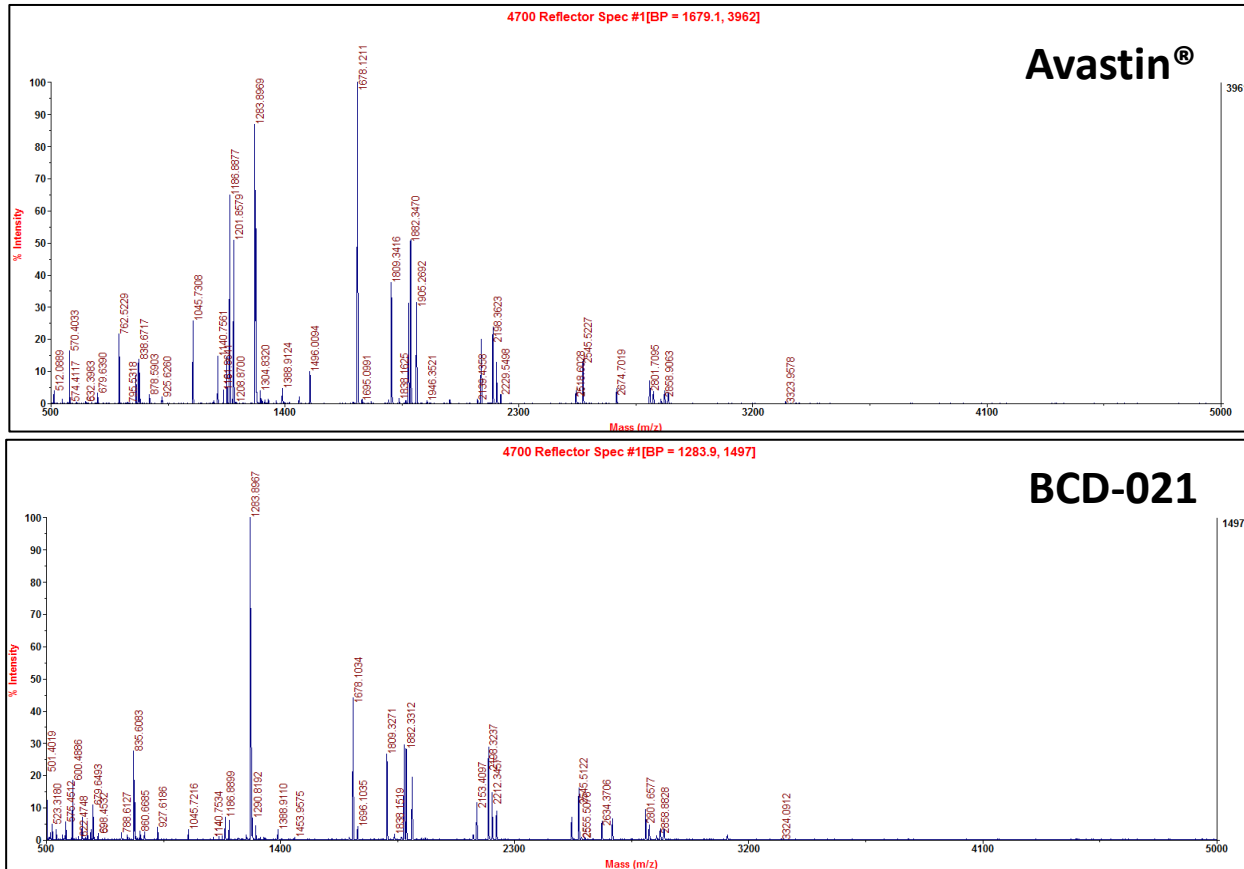
characterization *(electrophoretic pattern, liquid chromatographic pattern, Isoform pattern, spectroscopic profiles, peptide mapping, amino acid sequencing, mass spectrometry analysis, glycosylation analysis)*

(4) Immunochemical properties (binding to purified antigen)

(5) Biological activity

COMPARABILITY EXERCISE**Peptide fingerprint of the light chains by MALDI MS (Q1 2016)**

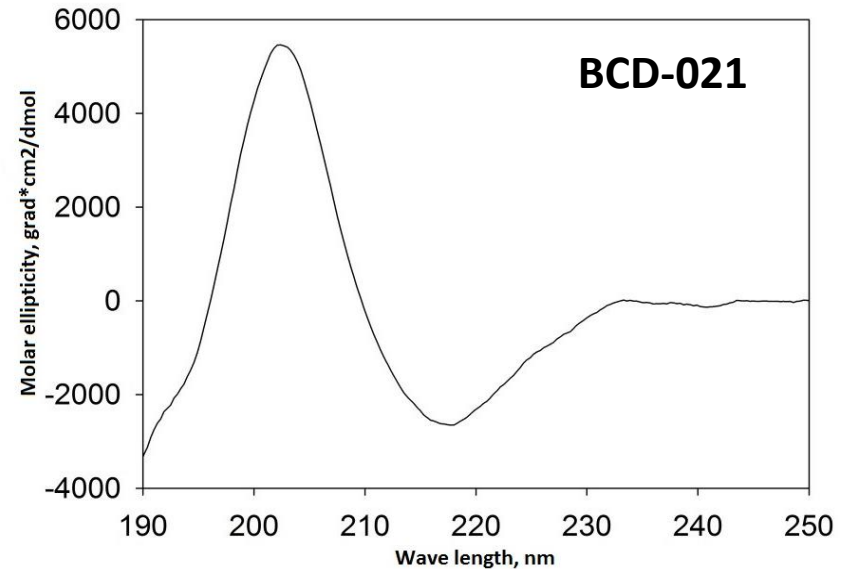
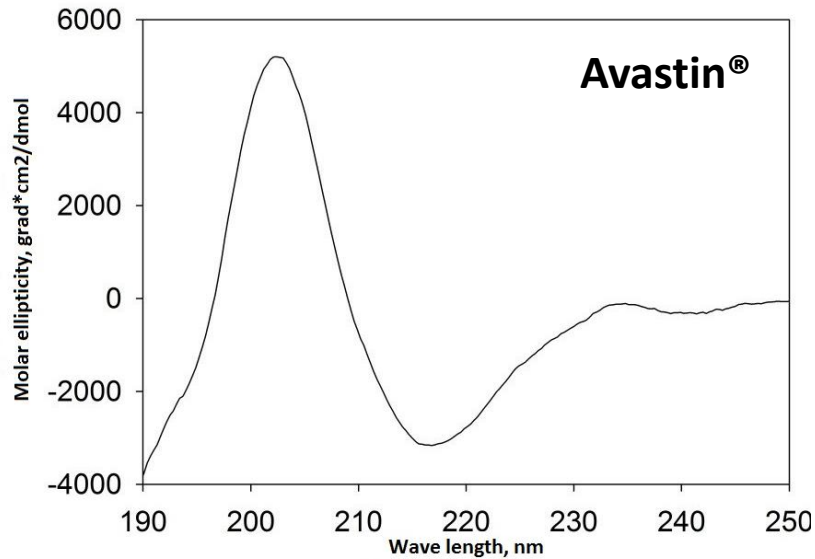
Corresponds to the light chain of the human kappa immunoglobulin

COMPARABILITY EXERCISE**Peptide fingerprint of the heavy chains by MALDI MS (Q1 2016)**

Corresponds to the heavy chain of the human kappa immunoglobulin

COMPARABILITY EXERCISE

Secondary structure by far UV circular dichroism (Q1 2016)

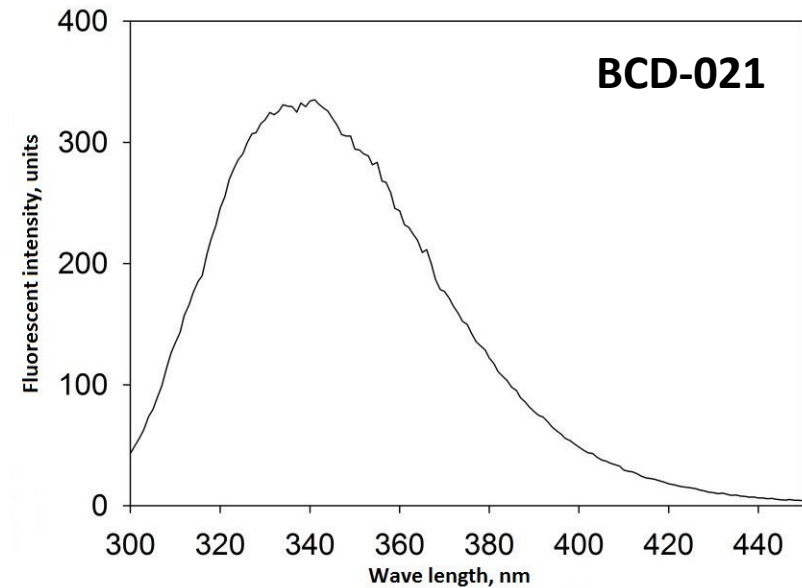
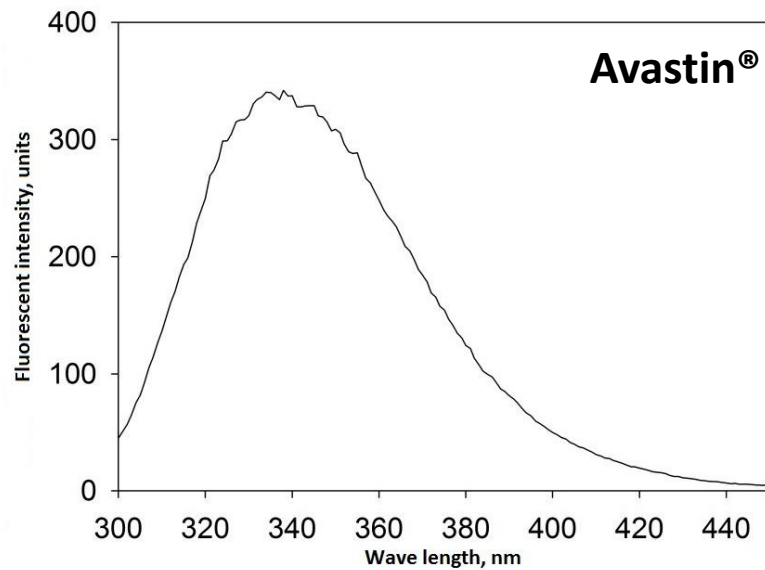


Far UV CD spectra of Avastin® and biosimilar bevacizumab are highly similar

(α -helix – 5 %, β -sheet – 60 % and random coil structures – 35 %)

COMPARABILITY EXERCISE

Tertiary structure by fluorescence (Q1 2016)



Fluorescence spectra of Avastin® and biosimilar bevacizumab are highly similar

Identity

Glycosylation profile: monosaccharides

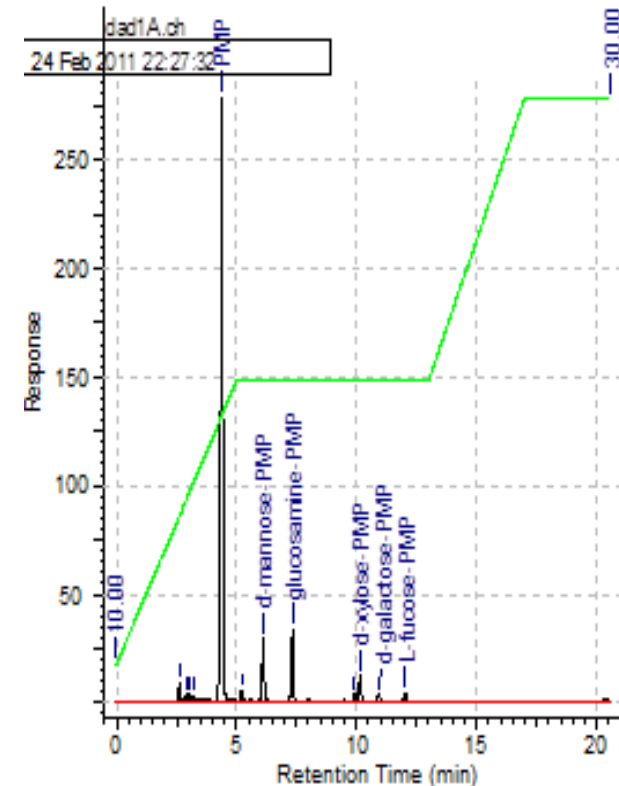
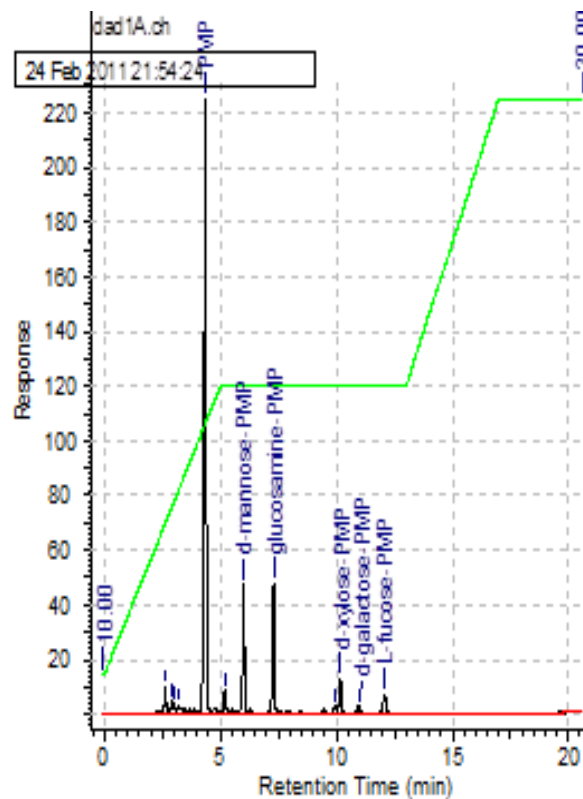


Reverse phase HPLC

(Agilent 1100, Column Luna C₁₈ 0.46 × 25 cm, 5 μm)

BCD-022

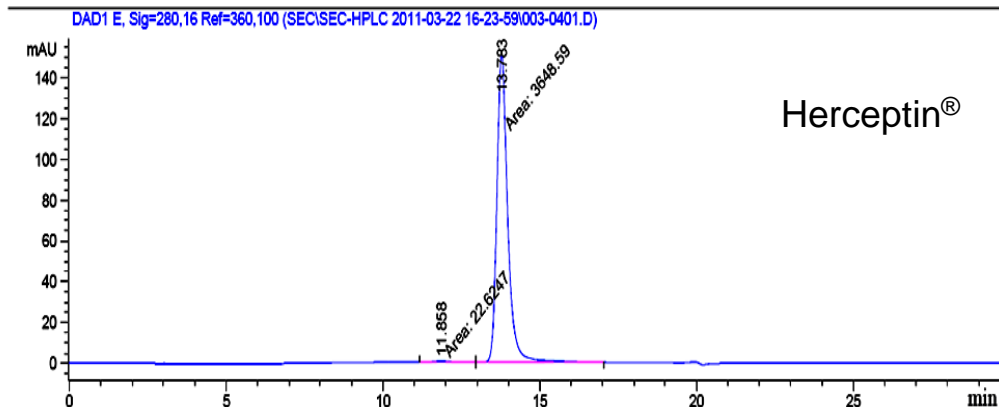
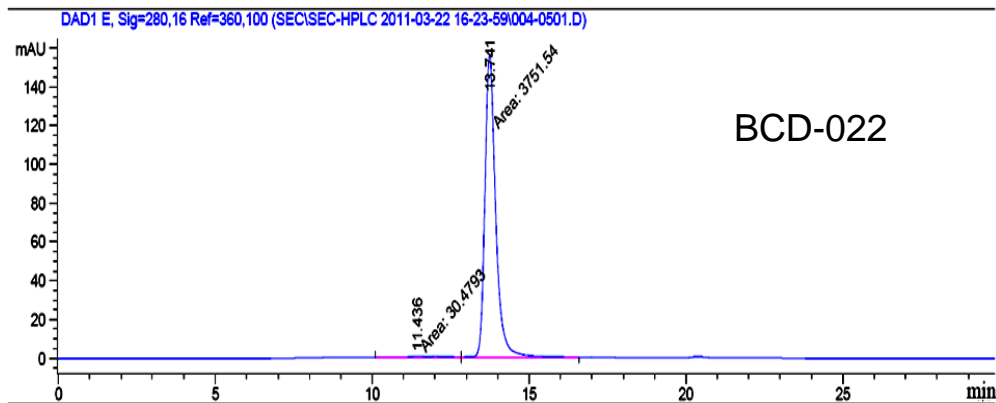
Herceptin®



BCD-022 (trastuzumab) and Herceptin® have comparable monosaccharide profile

Size exclusion HPLC

(Agilent 1100, column TSK Super SW 3000 (4.6 × 300)).



Purity, %

batch #	BCD-022	Herceptin®
1	99.2	99.3
2	98.9	99.2

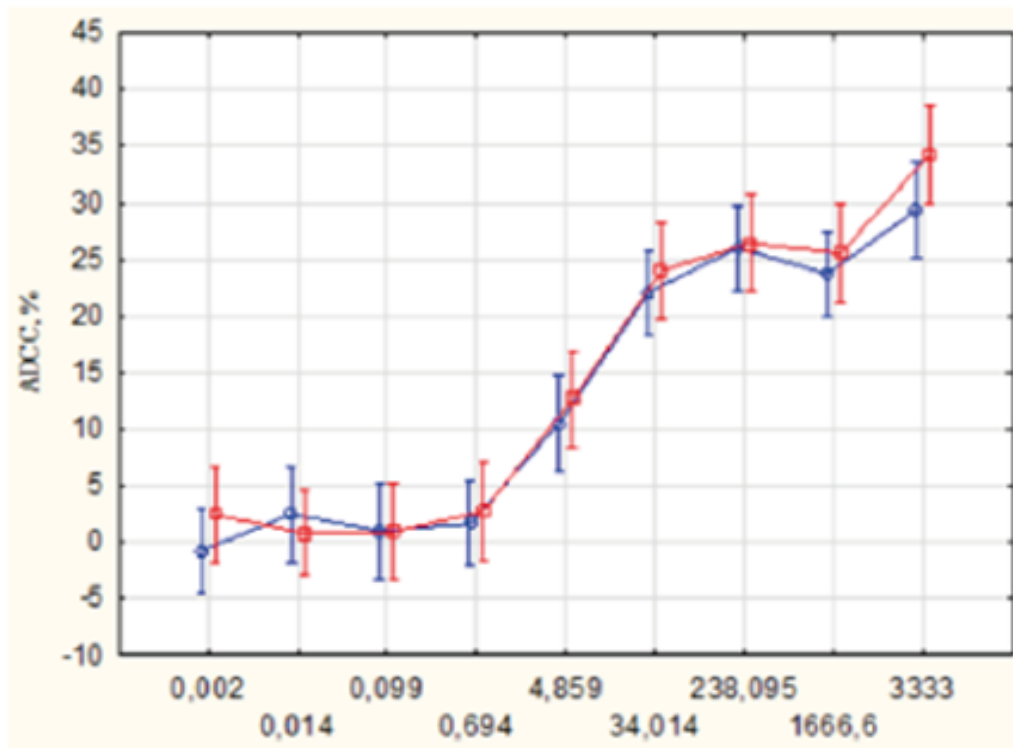
Conclusion: purity of BCD-022 is comparable to that of Herceptin®.

Citotoxicity (Rituximab)

COMPARABILITY EXERCISE

Antibody-dependent cell-mediated cytotoxicity of rituximab biosimilar

Antibody-dependent cellular cytotoxicity (WIL2-S cells +PBMC cells)



Blue line – Acellbia®
Red line - MabThera®

Non-clinical studies

Pharmacokinetics after repeated administration

Design:

Type of administration:

repeated IV weekly infusions
for 12 weeks

Animals: *Macaca mulatta* (22
animals)

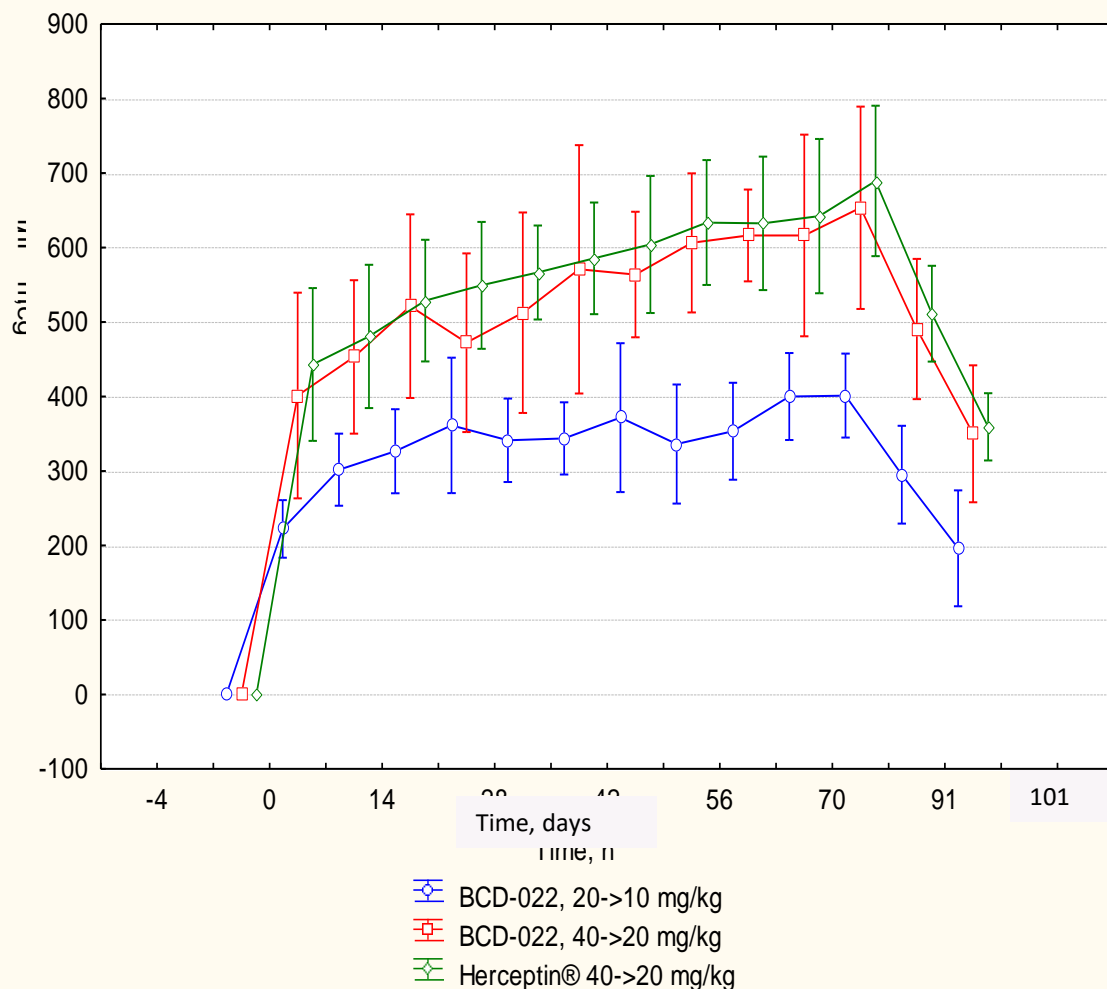
Groups:

- Control
- Herceptin® 40 mg/kg
- BCD-022 40 mg/kg –
loading dose, 20 mg/kg
maintenance dose
- BCD-022 20 mg/kg –
loading dose, 10 mg/kg
maintenance dose

Blood sampling points:

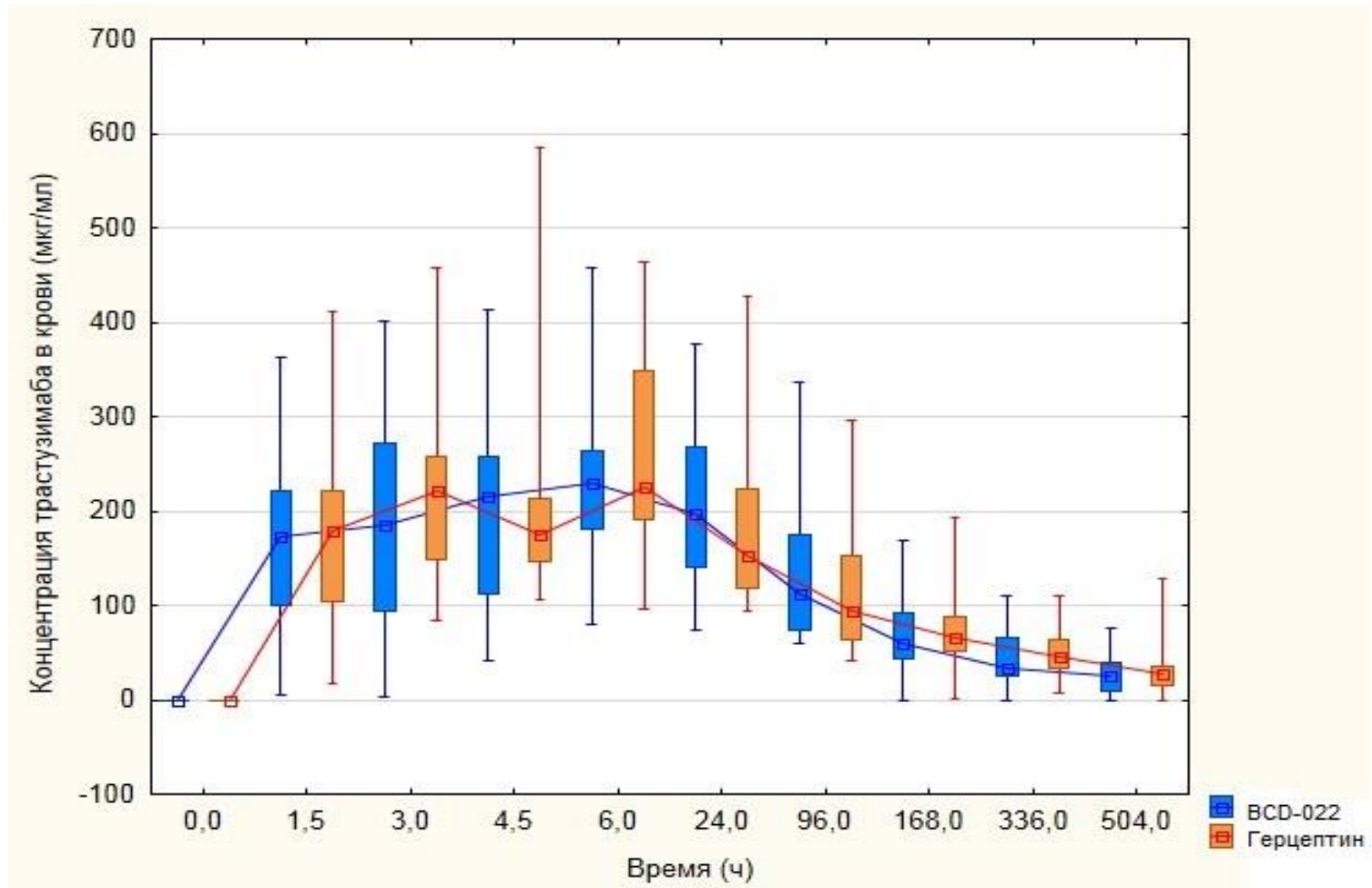
0; 3; 7; 10; 14; 17; 21; 24; 28;
31; 35; 38; 42; 45; 49; 51; 56;
60; 63; 67; 70; 74; 77; 81; 91
and 101 days after the first
drug administration

Results:



PHASE I - Clinical study

Pharmacokinetics:



PHASE III - Clinical study



BCD-022-02

Multicenter randomized double-blind phase III clinical trial comparing safety and efficacy of BCD-022 (CJSC BIOCAD, Russia) used with paclitaxel to Herceptin[®] (F. Hoffmann-La Roche Ltd, Switzerland) used with paclitaxel in the first-line treatment of **HER2-positive metastatic breast cancer patients**

Data exclusivity



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- ❑ **8 years for reference products**, for which a marketing authorization has been granted in the EU

- ❑ **Complete dossiers:**
 - ✓ Safety and Efficacy data
 - ✓ Preclinical and Clinical studies



Data exclusivity

- ❑ Biosimilar applications cannot rely on the reference product's data until the protection period expires



Data protection

- ❑ **4 years for innovator biologics**, counted from the day of approval by the FDA
 - ✓ Biosimilar applications cannot be filled in the FDA during this period

- ❑ **Originator's complete dossier:**
 - ✓ Safety and Efficacy data
 - ✓ Preclinical and Clinical studies



Market Exclusivity

Reference Product

- 12 years for innovator biologics,**
from the FDA approval date
- + 6 months** if pediatric clinical
studies are conducted
- ✓ **Total = 12,5 years**



Exclusivity for First Interchangeable Biologic

- ❑ **1 year** after the first commercial marketing approval date
- ❑ **18 months** after final court decision (all patent litigations)
- ❑ **18 months** after dismissal of legal action (patent rights)
- ❑ **42 months** after FDA approval (ongoing patent litigations in place)
- ❑ **18 months** after FDA approval (no patent litigations in place)

Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues:

- ❑ Safety and efficacy of the biosimilar have to be justified or demonstrated separately for each claimed indication.
- ❑ Extrapolation depends on clinical experience, available literature data, and **whether or not the same mechanisms of action or the same receptor(s) are involved in all indications.**
- ❑ Possible safety issues in different subpopulations should be addressed.

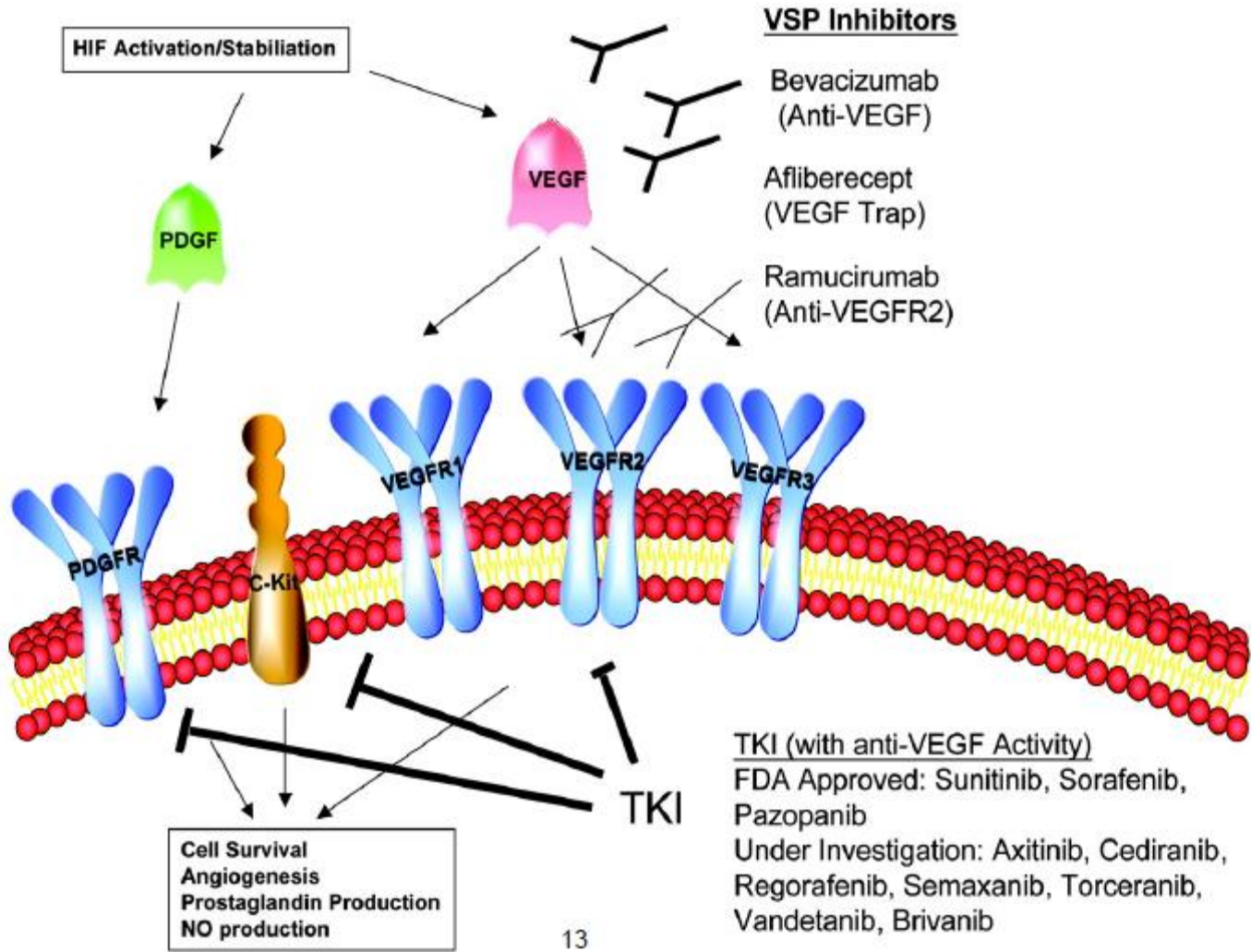
Extrapolation of Indications (US)

Justification for extrapolation should address:

- ❑ **the mechanism(s) of action in each condition of use (therapeutic indication)**
- ❑ the PK and bio-distribution in different patient populations
 - *relevant PD measures also may provide important information on the mechanism of action*
- ❑ differences in expected toxicities in each condition of use and patient population
- ❑ any other factor that may affect the safety or efficacy in each condition of use and patient population

Avastin® (Bevacizumab)

- Tumors release the VEGF protein causing nearby cells to sprout new vessels by angiogenesis.
 - New blood cells feed the tumor
- Bevacizumab is an angiogenesis inhibitor
 - Mechanism of action is by inhibiting vascular endothelial growth factor (VEGF)
 - Initially approved for colon cancer in 2004
 - Has been approved for us in other cancers such as: lung, renal, ovarian, glioblastoma



Interchangeability and substitution

European Union



EUROPEAN MEDICINES AGENCY
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- EMA does not have the authority to designate biosimilars as being interchangeable. Decisions are taken in national level by each member state.

United States



- BPCI Act empowers the FDA with authority to designate a biosimilar as interchangeable, but there are not specific requirements released yet.

Brazil

- Interchangeability is predicted in current legislation, but depend on specific guidelines to be issued by ANVISA.
- Equivalence Phase III clinical studies (head-to-head) is liked to be a requirement for substitution criteria and “interchangeable status”.
 - Non-inferiority clinical studies are not being accepted for the development of biosimilars deemed to be interchangeable with reference product.

FINAL THOUGHTS

- Patients' access to quality, safe and effective biosimilars still depend on additional regulations and guidelines.
- Harmonization and convergence efforts shall continue to facilitate the global development and access to biosimilars.
- Rules for data protection and market exclusivity should be improved to encourage innovation, but do not block biosimilars development and market access to high-cost medicines.
- Scientific knowledge and innovative analytical techniques should continue to drive new legislations and guidelines for biosimilars.

THANK YOU!

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