Building a Biosimilar Medicine

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prIME oncology

Learning Objectives

1. Explain the developmental and regulatory pathway for biosimilars and discuss how this differs from other medicines
2. Assess the regulatory, legislative, and economic considerations associated with the use of biosimilars in the United States, including the impact on cost and appropriate naming conventions
3. Evaluate current clinical trial evidence regarding the efficacy and safety of biosimilars for the treatment of breast cancer and lymphoma

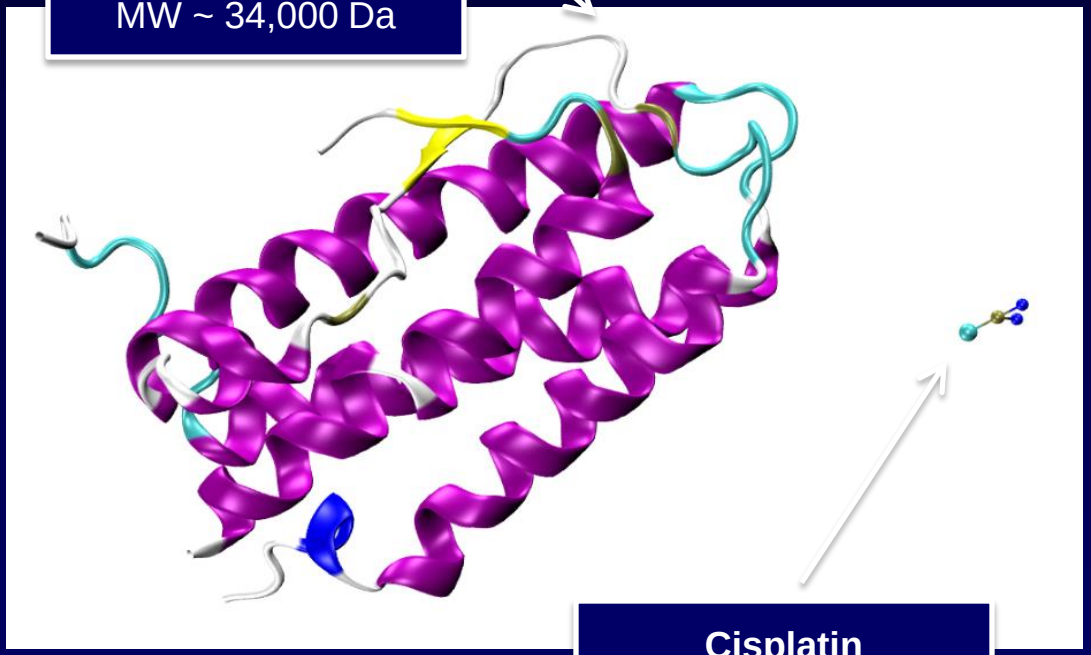
Biosimilar Definitions by Regulatory Agencies

- US Food and Drug Administration (FDA)
  - A biological product that is highly similar to a US-licensed reference biological product notwithstanding minor differences in inactive components, and for which there are no clinically meaningful differences in safety, purity, or potency of the product
- European Medicines Agency (EMA)
  - …structurally highly similar versions of an already authorized biological medicinal product (the reference product) with demonstrated similarity in physicochemical characteristics, efficacy, and safety, based on a comprehensive comparability exercise

FDA Draft Guidance. Rockville, MD: Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research; U.S. Department of Health and Human Services, Food and Drug Administration; 2012. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf
Weise M, et al. *Nat Biotechnol*. 2011;29(8):690-693. Accessed November 3, 2014.

Biologics vs Small Molecule Drugs

Human EPO
165 amino acids
MW ~ 34,000 Da



Cisplatin
$(NH_3)_2PtCl_2$
MW ~ 300 Da

Biologics are far more complex than traditional small molecule drugs in:

- **Molecular weight**
- **Structure (tertiary and quaternary structures, post-translational modifications)**
- **Manufacturing/production process**
- **Immunogenicity**

Courtesy of: Olgun Guvench, MD, PhD, University of New England College of Pharmacy

Biologics Have a Complex Manufacturing Process

The final biologic product is highly dependent on the manufacturing process:

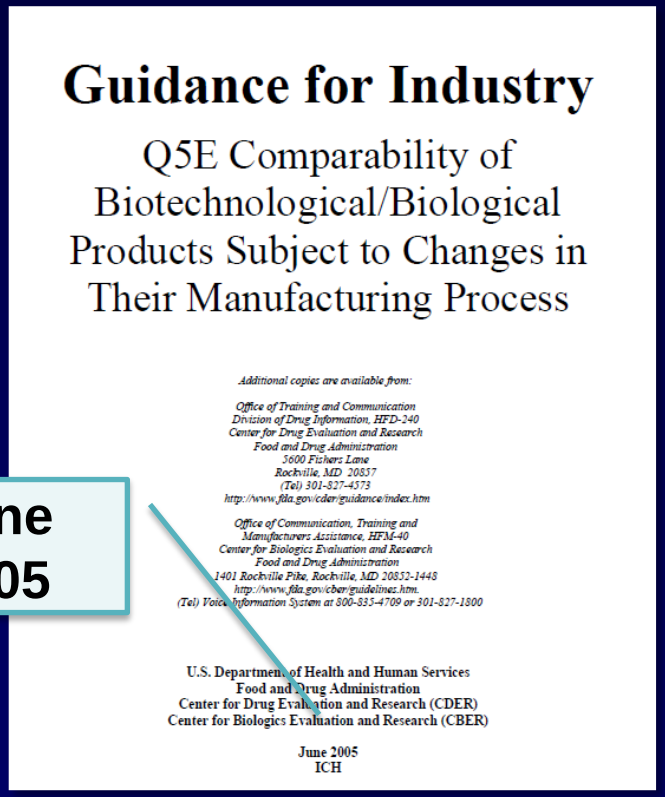
1. Clone DNA into vector
2. Transfer DNA into host cell for expression
3. Cell expansion
4. Cell production in bioreactors
5. Recovery of biologic
   - Filtration
   - Centrifugation
6. Purification through chromatography
7. Characterization and stability

Mellstedt H, et al. *Ann Oncol.* 2008;19(3):411-419.

Biologic Manufacturing Changes

INTRA-Manufacturer

INTER-Manufacturer



Guidance for Industry

Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

Office of Communication, Training and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
(Tel) Voice Information System at 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2005
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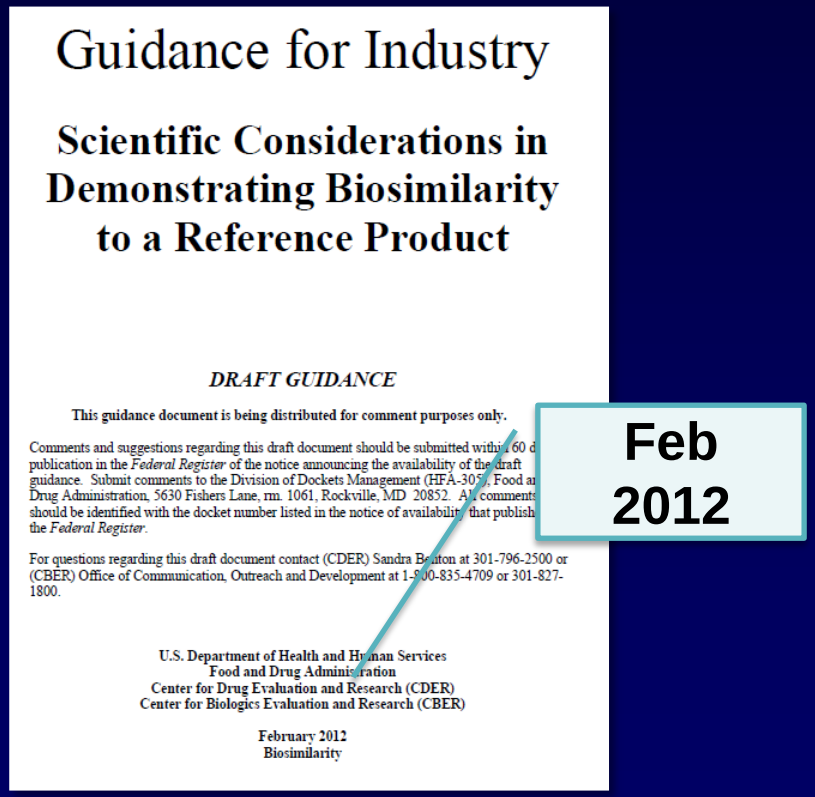


Guidance for Industry

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 d publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food a Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publish the *Federal Register*.

For questions regarding this draft document contact (CDER) Sandra Benton at 301-796-2500 or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2012
Biosimilarity

Feb 2012

Guidance for Industry: Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. US Food and Drug Administration. 2005. Available at: www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128076.pdf. Accessed November 22, 2011. FDA Draft Guidance. Rockville, MD: Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research; U.S. Department of Health and Human Services, Food and Drug Administration; 2012. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed November 5, 2014.

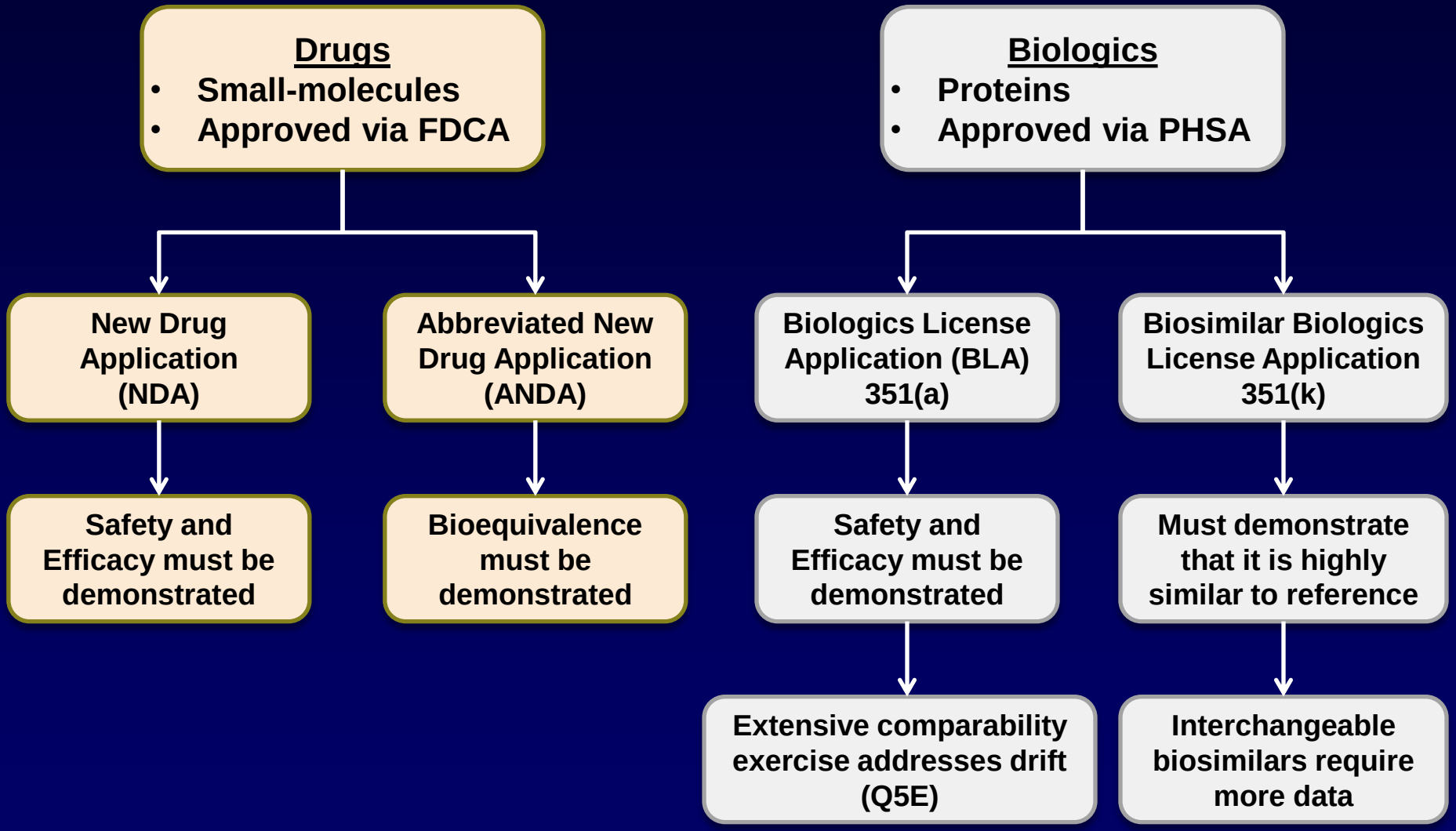
Pathway for Biosimilars in the US

- Two federal laws for the approval of pharmaceuticals in the United States
  - Food, Drug, and Cosmetic Act (FDCA)
    - New drug application (NDA)
    - Drug Price Competition and Patent Term Restoration Act of 1984 (informally known as Hatch-Waxman Act) created generic pathway
  - Public Health Service Act (PHSA)
    - Biologics License Application (BLA)

- Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010 (the Healthcare Reform Law)
  - Subtitle called the Biologics Price Competition and Innovation Act of 2009
  - Amends the Public Health Service Act to define an abbreviated application process for biosimilars

Zelenetz AD, et al. *J Natl Compr Canc Netw.* 2011; 9(Suppl 4):S1-S22.

Pathways for Approval in the USA



Demonstrating Biosimilarity: General Principles

- The clinical efficacy and safety of the biologic molecule has already been demonstrated (ie, by the innovator)
- The biosimilar sponsor only requires evidence that the candidate biosimilar is not significantly different from the reference product
  - Goal is not to replicate unnecessary clinical trials
  - Smaller-scale direct comparisons and extrapolation
- When a biosimilar is approved, there should not be an expectation that there will be differences in safety and efficacy

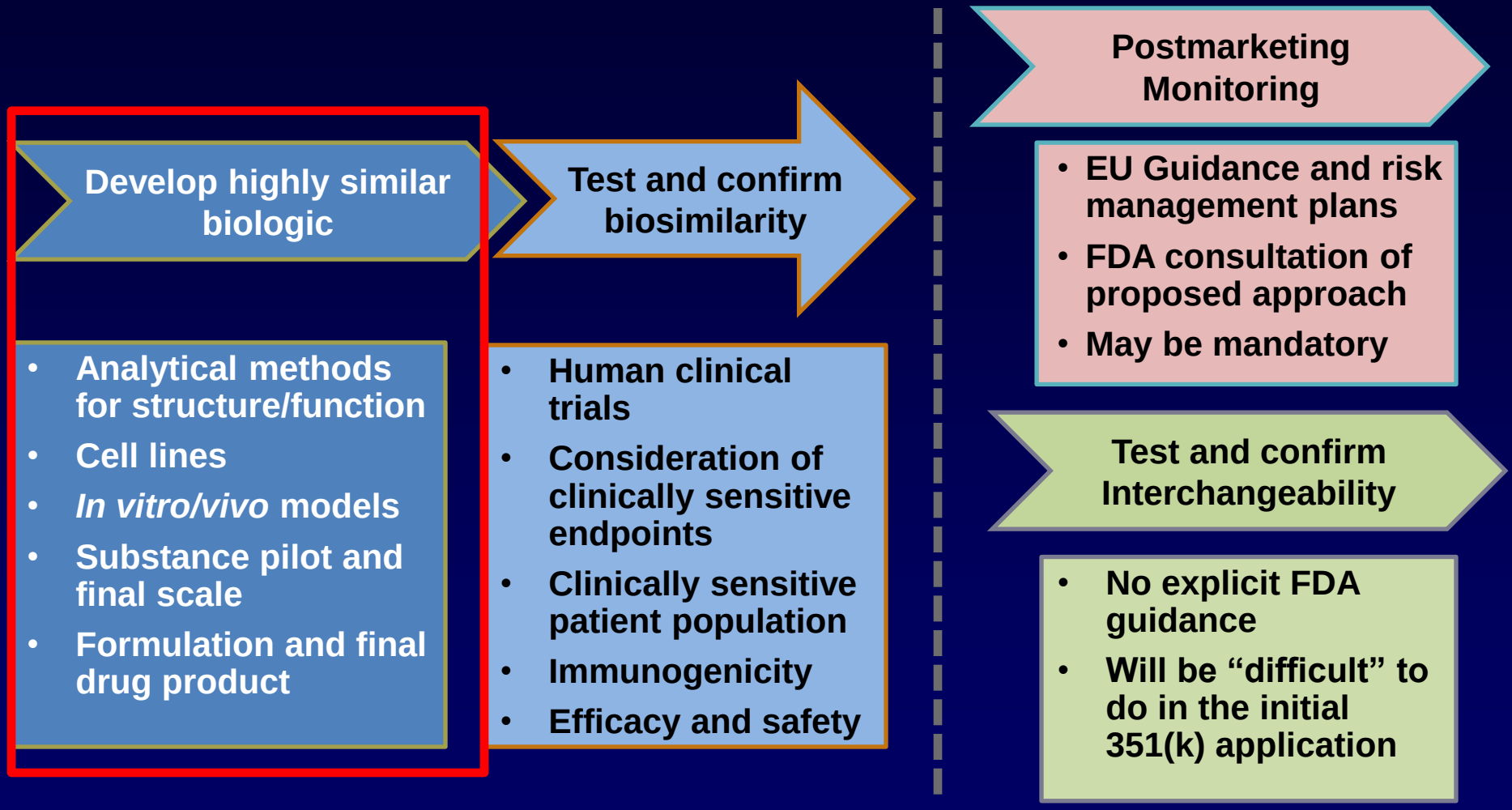
FDA Draft Guidance. Rockville, MD: Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research; U.S. Department of Health and Human Services, Food and Drug Administration; 2012. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed November 5, 2014.

Demonstrating Biosimilarity: A Stepwise Approach

- Compare proposed biosimilar to reference in terms of:
  1. Structure
  2. Function
  3. Animal Toxicity Studies
  4. Human Pharmacokinetics (PK) and Pharmacodynamics (PD)
  5. Clinical Immunogenicity
  6. Clinical Safety and Effectiveness
- FDA intends to utilize a "totality of the evidence" approach

FDA Draft Guidance. Rockville, MD: Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research; U.S. Department of Health and Human Services, Food and Drug Administration; 2012. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed November 5, 2014.

Biosimilar Development Approach



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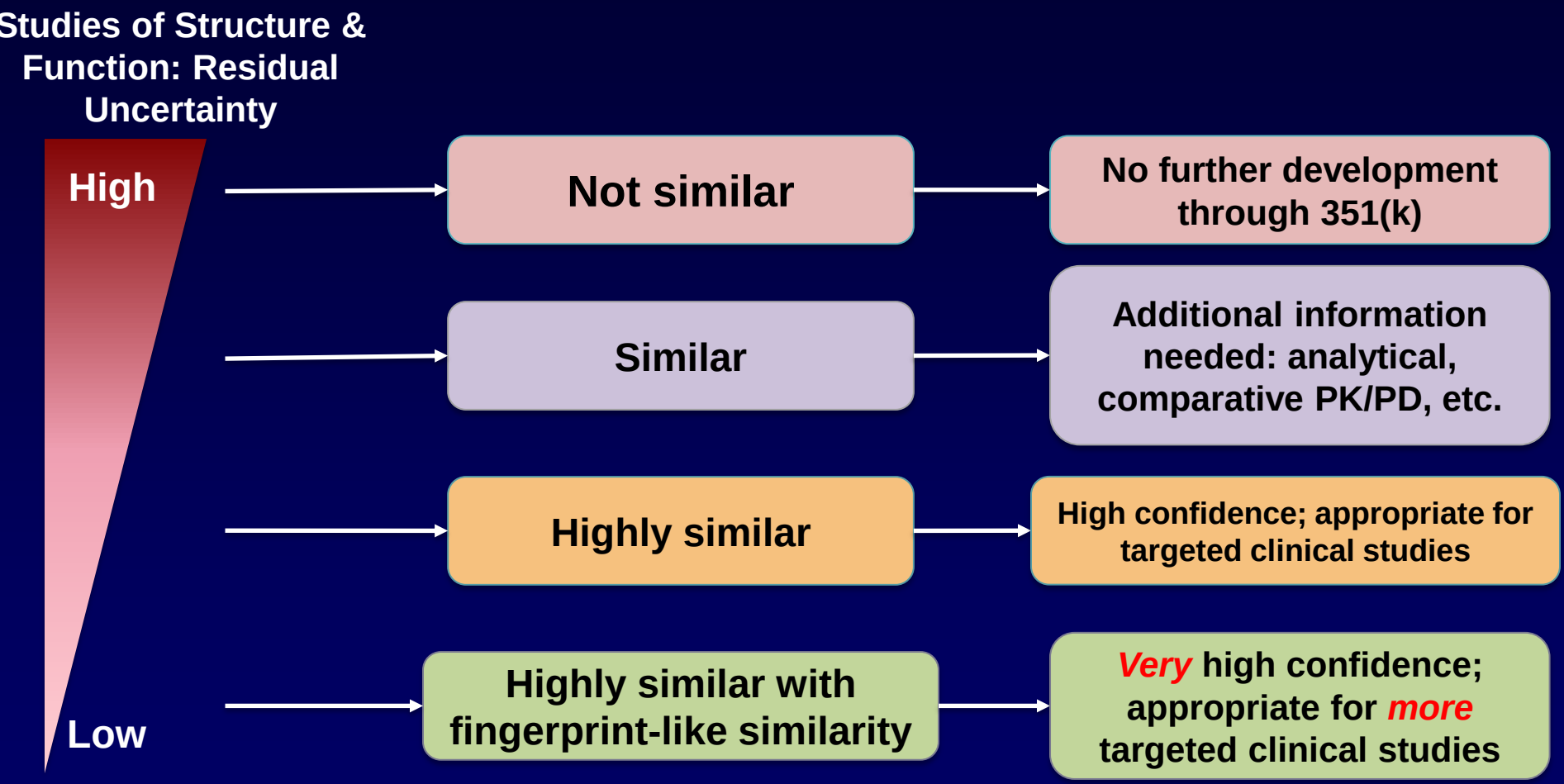
Structure and Function

- Serve as the “foundation” of biosimilar development
- Useful in determining what future studies are necessary
- Structure
  - Amino acid sequence, higher-order structures, glycosylation, pegylation, etc
  - Analyze lot-to-lot variability
- Function
  - Evaluate pharmacologic activity via *in vitro* or *in vivo* experiments
  - Functional evaluation that compares candidate to reference

FDA Draft Guidance. Rockville, MD: Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research; U.S. Department of Health and Human Services, Food and Drug Administration; 2012. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed November 5, 2014.

Four Assessments of Analytical Characterization



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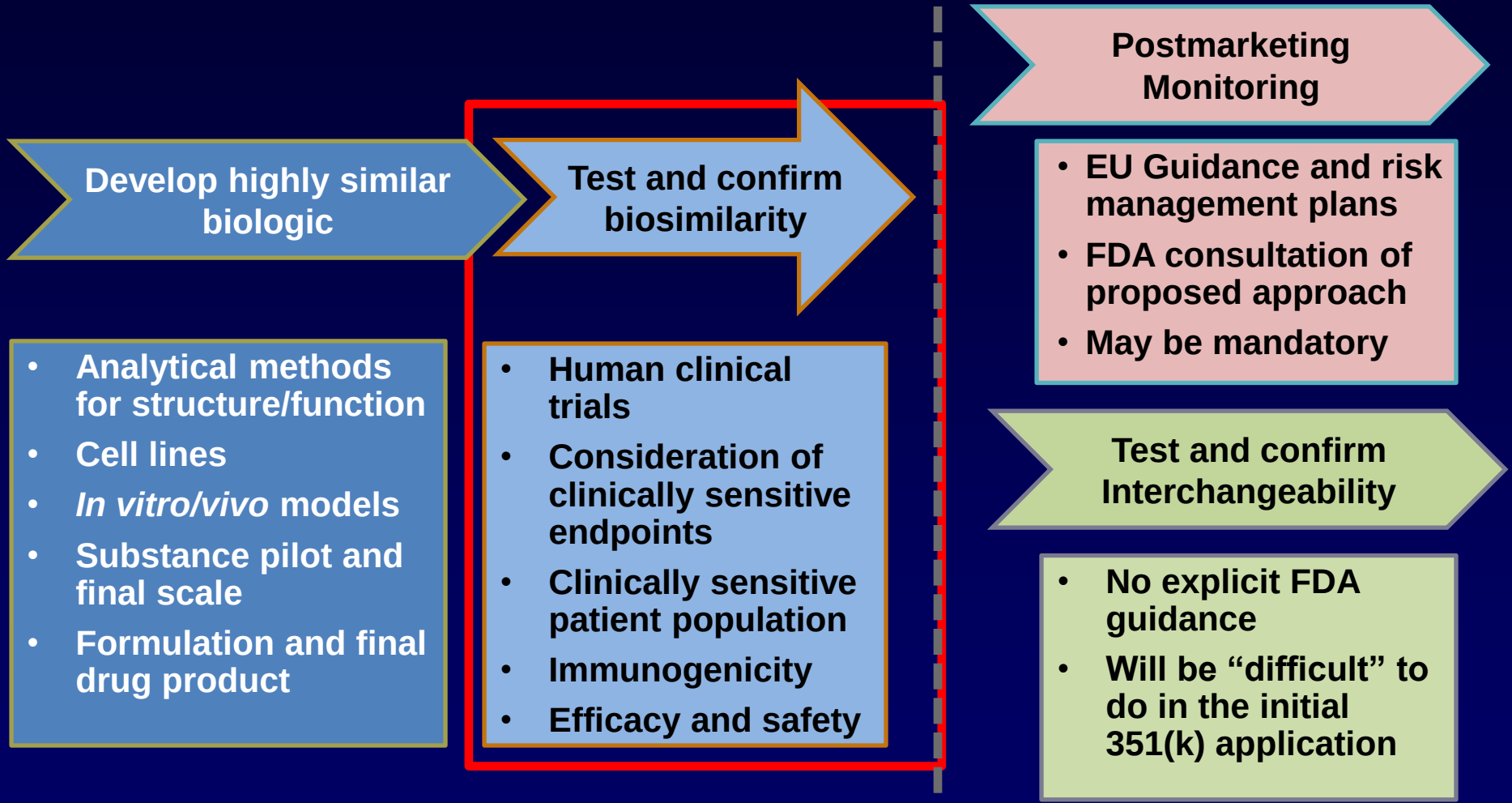
Biosimilar Development Approach



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Human Pharmacokinetics & Pharmacodynamics: FDA

- "Fundamental" for demonstrating biosimilarity
- Both PK and PD will be necessary
  - PK: Patient population considerations
  - PD should study measures that are:
    - Relevant to clinical outcomes
    - Can be quickly assessed with precision
    - Has the sensitivity to detect clinically meaningful difference
- Ideally correlate exposure to clinical outcomes

FDA Draft Guidance. Rockville, MD: Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research; U.S. Department of Health and Human Services, Food and Drug Administration; 2012. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed November 5, 2014.

EMA Guidance: G-CSF

- **Pharmacokinetics:**
  - **Single dose crossover design using SC and IV administration**
  - **Primary endpoint: AUC**
  - **Secondary endpoints: Cmax and half-life**
  - **General principles for demonstration of bioequivalence are applicable**
- **Pharmacodynamics:**
  - **ANC relevant PD marker for G-CSF**
  - **Compare biosimilar to reference in healthy volunteers**
  - **CD34 count secondary endpoint**

Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues. London: Committee for Medicinal Products for Human Use; European Medicines Agency; 2006. Available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003955.pdf. Accessed November 5, 2014.

Clinical Studies: FDA

- **Clinical Immunogenicity**
  - **Goal is to evaluate potential differences in incidence and severity of immune responses using endpoints such as antibody formation (binding, neutralizing), cytokine levels, etc**
  - **FDA recommends a comparative parallel study**

- **Efficacy & Safety: Specific clinical trial design will depend on what residual questions remain**
  - **Clinical studies should be designed to demonstrate neither *decreased nor increased* activity**
  - **Use clinically relevant and sensitive endpoints in the right population**

Schellekens H. *NDT Plus*. 2009;2(Suppl 1):i27-i36.

EMA Guidance: G-CSF

- **Clinical efficacy studies**
  - **Many indications recognized**
  - **"Recommended" model is prophylaxis of severe neutropenia following cytotoxic chemotherapy known to cause severe neutropenia in a homogenous patient group, emphasis on 1st chemo cycle**
  - **Two-arm comparability design if one chemotherapy regimen used and frequency/duration of neutropenia is well known**
  - **Three arms (with placebo) may be needed if other chemo regimens used**
  - **Sponsor to justify comparability delta**
  - **Allows extrapolation to other indications of the reference product if the MOA is the same**

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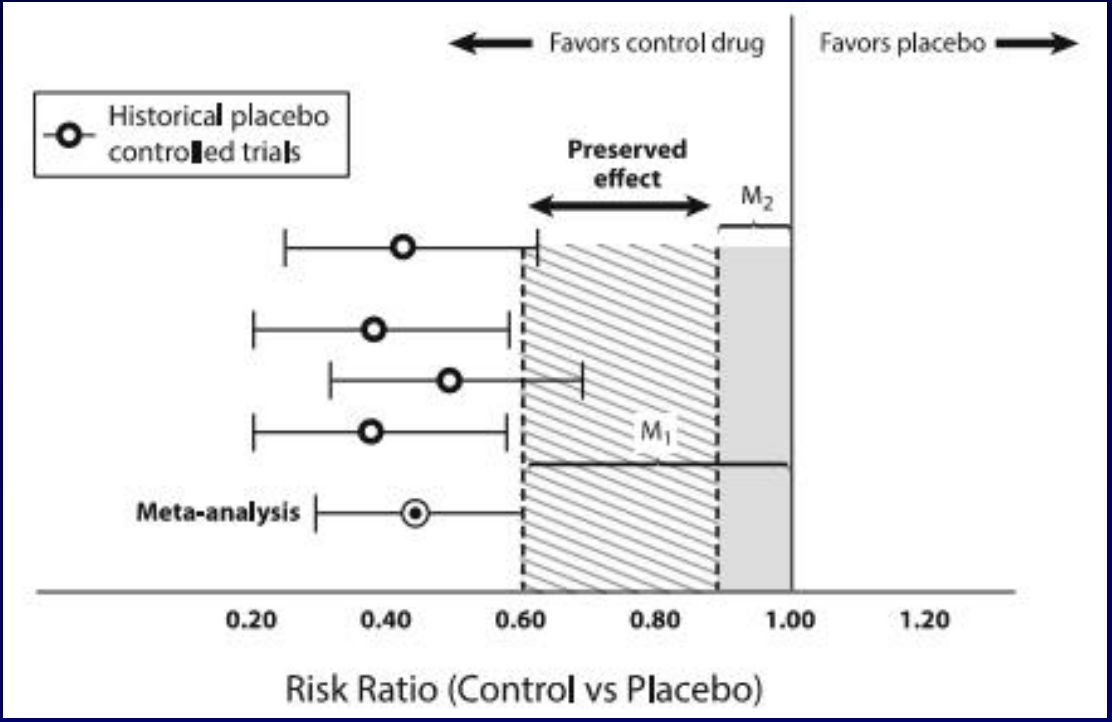
Clinical Trial Design: Equivalence

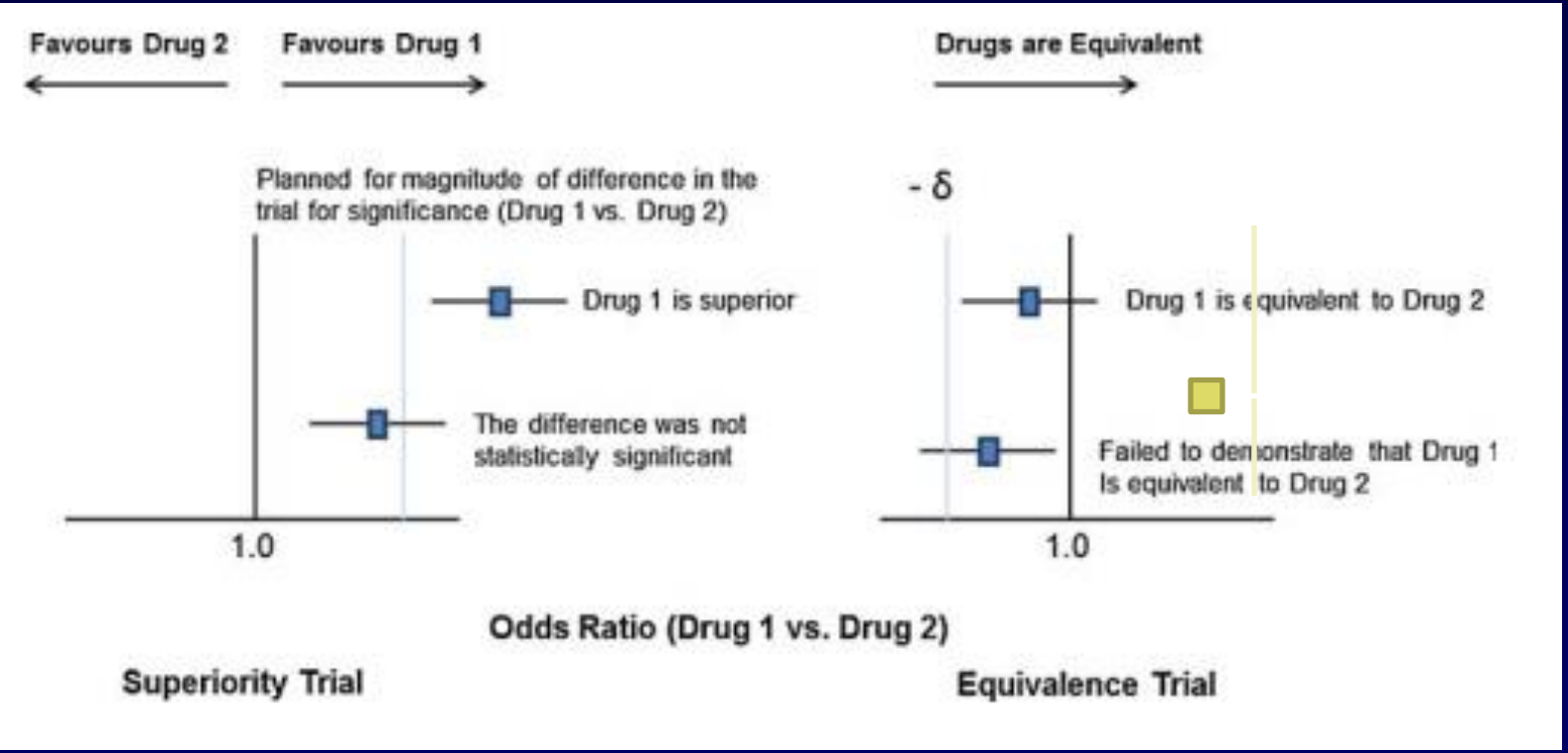
- **Establishing the equivalence margin (comparability delta - δ) via the 95-95 method**



Dranitsaris G, et al. *Invest New Drugs*. 2013;31(2):479-487.

Clinical Trial Design: Equivalence

- **Null hypothesis: The biosimilar and the reference product are not equivalent (biosimilar is better or worse)**
- **Alternative hypothesis: Biosimilar and reference are equivalent**



Dranitsaris G, et al. *Invest New Drugs*. 2013;31(2):479-487.

EMA Guidance: G-CSF

- **Clinical safety**
  - **Collect data from repeat dosing preferably in a comparative clinical trial**
  - **Total exposure should correspond to routine clinical practice**
  - **Total follow-up for at least 6 months**
  - **Adequate numbers to asses bone pain and laboratory abnormalities**
  - **Immunogenicity data to be collected**

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Biosimilar Development Approach

Develop highly similar biologic

- Analytical methods for structure/function
- Cell lines
- *In vitro/vivo* models
- Substance pilot and final scale
- Formulation and final drug product

Test and confirm biosimilarity

- Human clinical trials
- Consideration of clinically sensitive endpoints
- Clinically sensitive patient population
- Immunogenicity
- Efficacy and safety

Postmarketing Monitoring

- EU Guidance and risk management plans
- FDA consultation of proposed approach
- May be mandatory

Test and confirm Interchangeability

- No explicit FDA guidance
- Will be “difficult” to do in the initial 351(k) application

FDA Approval

Adapted from: McCamish M, et al. *Clin Pharmacol Ther*. 2012;91(3):405-417.
FDA Draft Guidance for Industry. Rockville, MD: Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research; U.S. Department of Health and Human Services, Food and Drug Administration; 2012. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf. Accessed November 5, 2014.

Interchangeability

- Safety standards for determining interchangeability
  - Must be a biosimilar
  - Produces same clinical result as the reference in any given patient
  - Risk of safety or diminished efficacy due to alternating or switching between biosimilar and reference is no more than using the reference product with no switching
- Will be “difficult” in the initial 351(K) application due to the sequential nature of the assessment
- Appropriate to be “substituted for the reference product without the intervention of the health care provider who prescribed the reference product”
- The study design to demonstrate interchangeability has not been fully determined

Chow SC, et al. *Stat Med.* 2013;32(3):442-428.

PHS Act, section 351(k)(4). Available at: www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/ucm216146.pdf. Accessed November 5, 2014.

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Post-Market Monitoring: EU Risk Management Plans

- "Comprehensive and proactive application of scientifically based methodologies to identify, assess, communicate, and mitigate risk throughout a drug's life cycle so as to establish and maintain a favorable benefit-risk profile."
- Mandatory for biologics (immune reactions)
- Four steps for a particular risk:

Step	Description	Risk Management Plan
1. Detection	Identify risk	Pharmacovigilance
2. Assessment	Understand/monitor risk	
3. Communication	HCP education	Risk minimization
4. Minimization	Act to reduce risk	

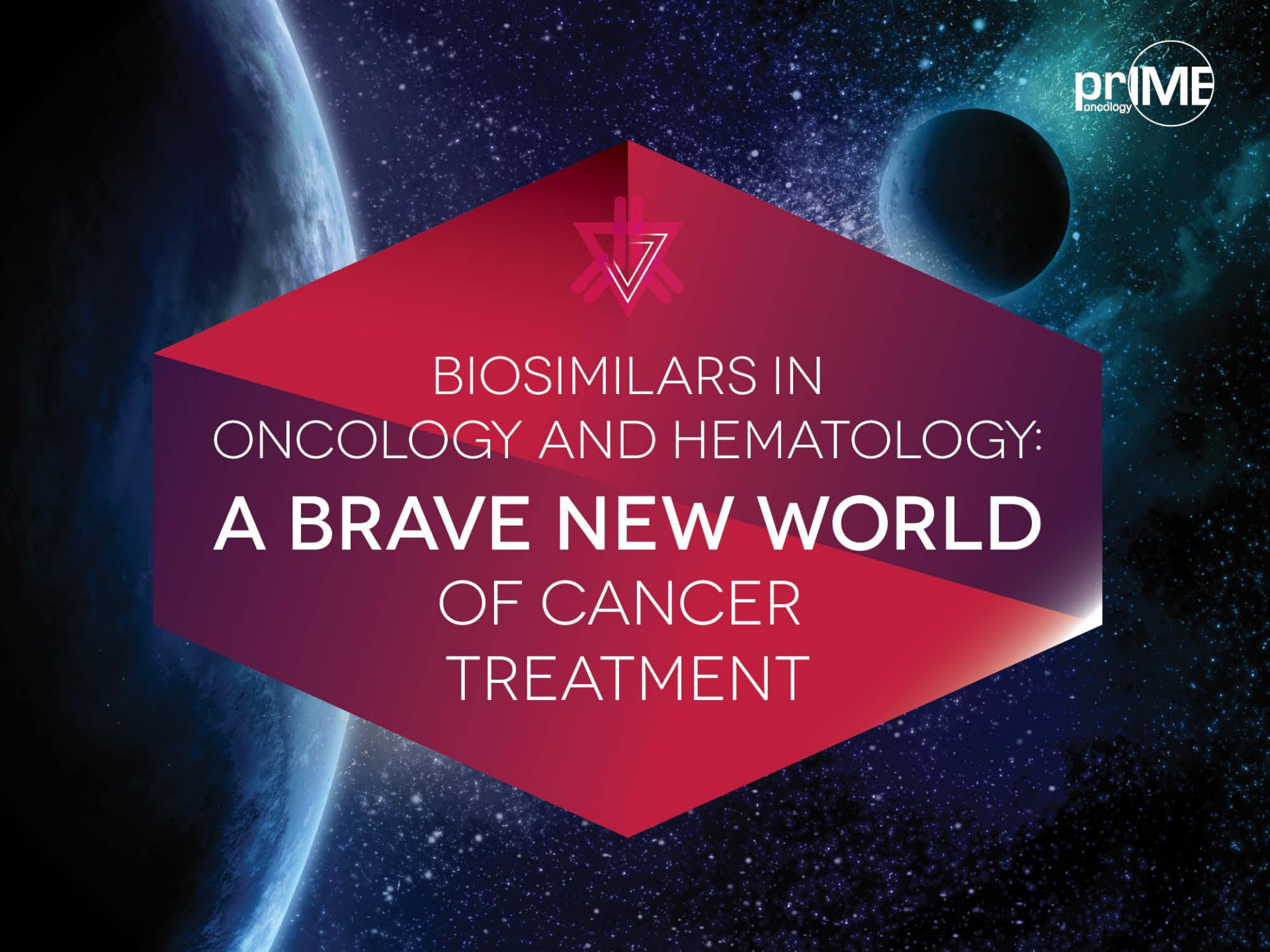
Zuñiga L, et al. *Pharmacoepidemiol Drug Saf*. 2010;19(7):661-669.

Pharmacovigilance: Challenges in the USA

- **Traceability and attribution**
  - **Naming**
  - **Codes: NDC vs HCPCS**
  - **The burden of correct attribution of safety signals is with the healthcare provider**
- **Data**
  - **Electronic health record**
  - **Prospective registries**
  - **Administrative claims**
  - **Linked databases**
- **Transitions of care**

Summary

- Biosimilars are not generic biologics
- The comparability exercise that allows a biosimilar to demonstrate that it is “highly similar” to a reference is scientific and robust
- Interchangeability and pharmacovigilance are challenges that need to be addressed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