A Brave New World of Biosimilars

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Disclosures

- The presenter and their preceptor have no financial relationships with any commercial interests pertinent to this presentation.

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Pharmacist & Nurse Objectives:

- Summarize the data requirements in the regulatory process of a biosimilar product
- Identify Food & Drug Administration (FDA) requirements for biosimilar interchangeability
- Recall pharmacovigilance efforts with biosimilar products

Pharmacy Technician Objectives:

- Outline differences between biosimilar and generic drugs
- Recall the complexity of the biosimilar manufacturing process
- Recognize the implications of biosimilar interchangeability

Background

Biologics

Biologics are a class of compounds produced using living organisms

- Bacterial, mammalian host cells

Many types of biological products approved for use in the US

- Therapeutic proteins (filgrastim), monoclonal antibodies (infliximab), vaccines (tetanus & influenza)

Cost of development has steadily increased over decades; takes 8-10 years on average

Source: Biosimilars. U.S. Food and Drug Administration; 2020.

What is a biosimilar?

- A biologic product which is highly similar to the reference product notwithstanding minor differences in clinically inactive components

- There must be no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product

Source: Biosimilars. U.S. Food and Drug Administration; 2020.

Background

First biosimilar approved for use in 2006 by the European Medicines Agency (EMA)

- 20 countries have since adopted regulatory framework

First FDA-approved biosimilar was in 2015

- Filgrastim biosimilar

Main barriers to adoption include the lack of education regarding the comparative safety and efficacy of the agent to the reference product, payer coverage, as well as national policy on substitution

Source: Raedler, L. A. (2016) *Am Health Drug Benefits*, *9,*150–154.
Source: Kang, et al. (2020). *Biologicals. 65*, 1–9.
Source: ASHP Advantage Media (2013).
Source: Araújo, F. C. (2016) *Current rheumatology reports*, *18*(8), 50.

How Did Biosimilars Come About?

Hatch-Waxman Act of 1984 did not apply to biologic agents

- Not economically feasible for biologics developers to bring competing biologics to market

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of the Affordable Care Act, which was signed into law in 2010

The BPCI Act amended the Public Health Service Act, and created an abbreviated licensure pathway for biological products shown to be biosimilar or interchangeable to an FDA-licensed biological reference product

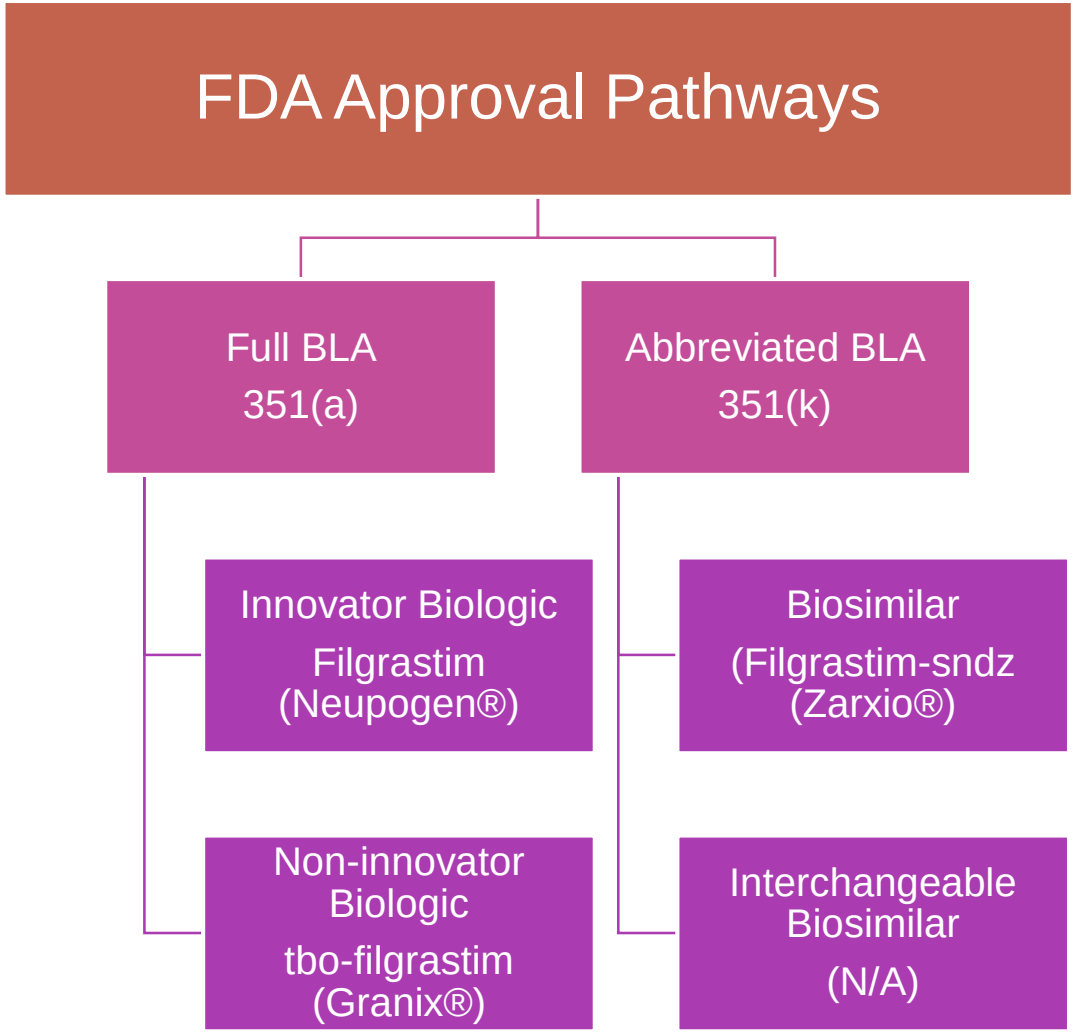
- 351 (k) Biologics Licensure Application (BLA)

Source: Zelenetz AD, et al. *J Natl Compr Canc Netw. 2011; 9(suppl 4):S1-22.*

Biologics Price Competition & Innovation Act of 2009

Application Type	Biologics license application (BLA) or biosimilar interchangeable license application
Sponsor Exclusivity	12 years of exclusivity for new biological structures once FDA approved; an additional 6 months if pediatric studies are conducted
Filing Limitations	Biosimilar applications can be filed 4 years after FDA product approval of Sponsor product
Generic exclusivity	No exclusivity for biosimilars • One year of exclusivity granted for the first interchangeable biosimilar

Source: Coggio, B.D., et al (2018) In: Gutka H., et al. Biosimilars.


FDA Approval Pathways
Full BLA
351(a)
Abbreviated BLA
351(k)
Innovator Biologic
Filgrastim
(Neupogen®)
Biosimilar
(Filgrastim-sndz
(Zarxio®)
Non-innovator
Biologic
tbo-filgrastim
(Granix®)
Interchangeable
Biosimilar
(N/A)

Are Biosimilars the Same as Generic Drugs?

While each are approved through abbreviated pathways, they are NOT the same!

Active ingredients of generic drugs are the same as the active brand product

- Generic = brand product

Biosimilar active ingredients are NOT the same as the active innovator product

- Products derived from different cell lines
- ‘Highly similar’ to innovator

Source: Biosimilars. U.S. Food and Drug Administration; 2020.

Generic Drugs Versus Biosimilar Agents

	Generic Drugs	Biosimilar
Time to develop	2 - 3 years	8 - 10 years
Cost to develop	$1 - 4 million	$100 - 250 million
Requirement for approval	Bioequivalence studies	Analytical, animal and clinical studies
Reference	Orange Book	Purple Book

Source: Araújo, F. C., et al (2016). *Curr Rheumatol Rep, 18*(8), 50.

Source: Biosimilar Development, Review, and Approval. U.S. Food & Drug Administration; 2017.

Generic Drugs Versus Biosimilar Agents

	Generic Drugs	Biosimilar
Structure	Simple	Complex
Size	Small, Low molecular weight	Large Protein, High molecular weight
Manufacturing Process	Predictable, controlled organic chemistry reactions - Small changes = less impact	Complex, involves unique living cell lines - Small changes = great impact
Immunogenicity	Low	High
Storage Requirements	High stability	Proteins typically vulnerable to environmental factors (temperature, light, moisture)

Source: ASHP Advantage Media (2013).

Recently Approved Biosimilar Agents

Biosimilar Name	Reference Product	Date of Approval	Interchangeable (Y/N)
Rituximab-arrx (Riabni®)	Rituximab (Rituxan®)	December 2020	No
Adalimumab-fkjb (Hulio®)	Adalimumab (Humira®)	July 2020	No
Pegfilgrastim-apgf (Nyvepria®)	Pegfilgrastim (Neulasta®)	June 2020	No
Infliximab-axxq (Avsola®)	Infliximab (Remicade®)	December 2019	No

Source: Biosimilar Product Information. U.S. Food and Drug Administration; 2020.

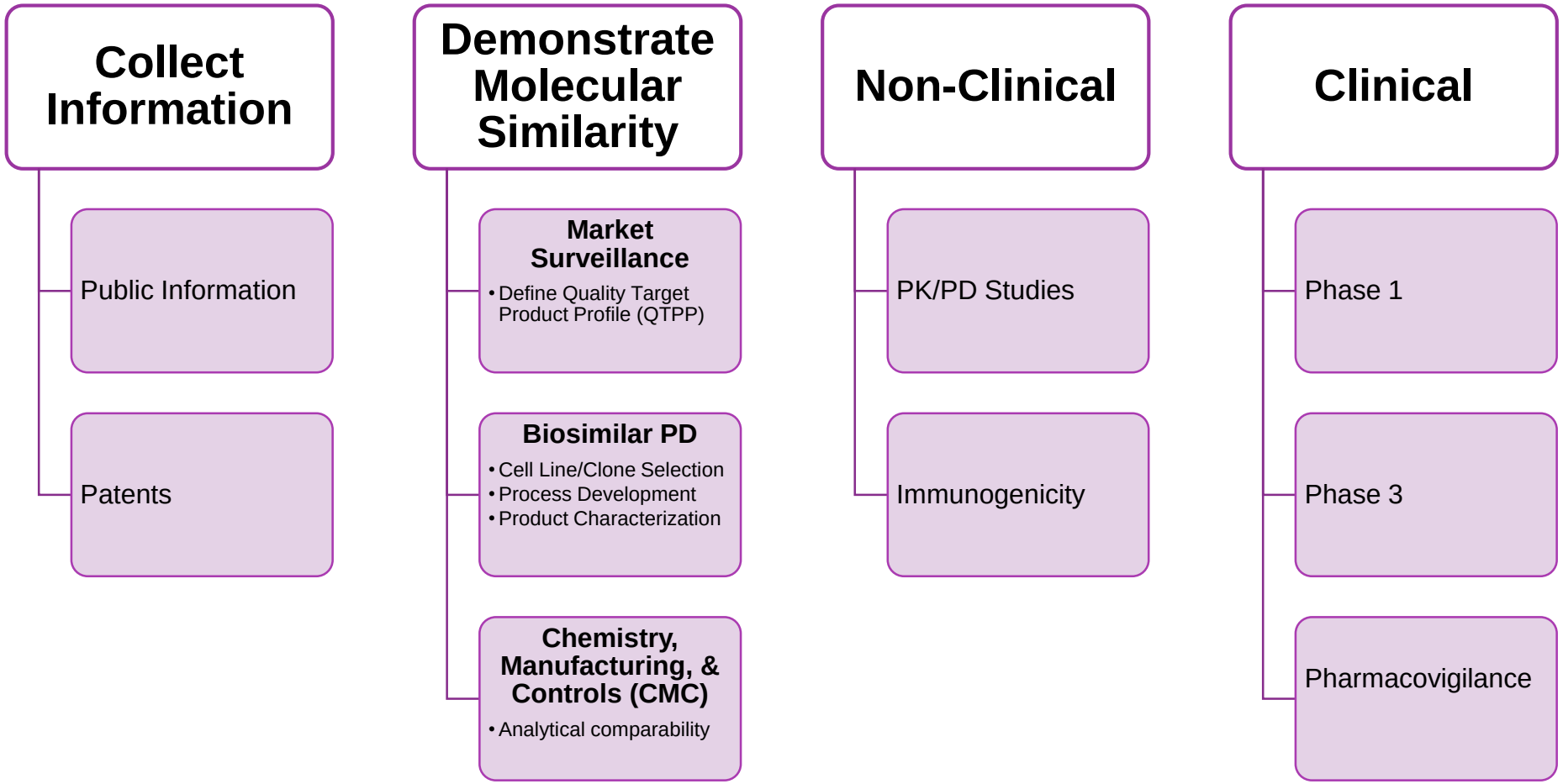
Biosimilar Cost Savings

- Biologics alone accounted for 38% of U.S. prescription drug spending in 2015[4]
  - High cost per dose
  - Accounted for 70% of drug spending growth over 5-year period[5]

- It is estimated that biosimilars will reduce direct drug spending by $54 billion from 2017 to 2026[6]

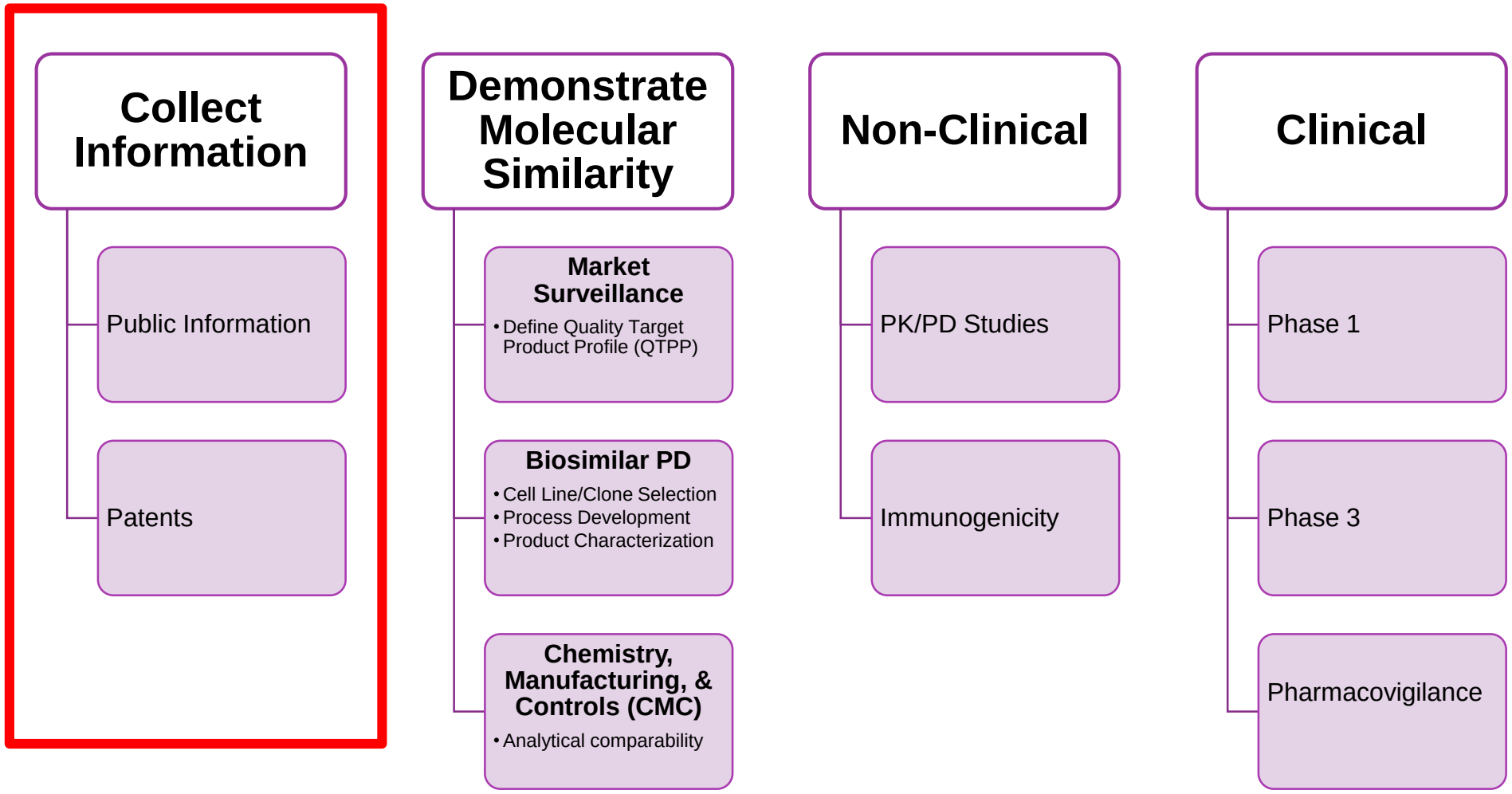
Biosimilar Development

Biosimilar Development



Source: Manzi A.E., et al (2018) In: Gutka H., et al. Biosimilars

Biosimilar Development



Source: Manzi A.E., et al (2018) In: Gutka H., et al. Biosimilars

Step 1: Collect Information

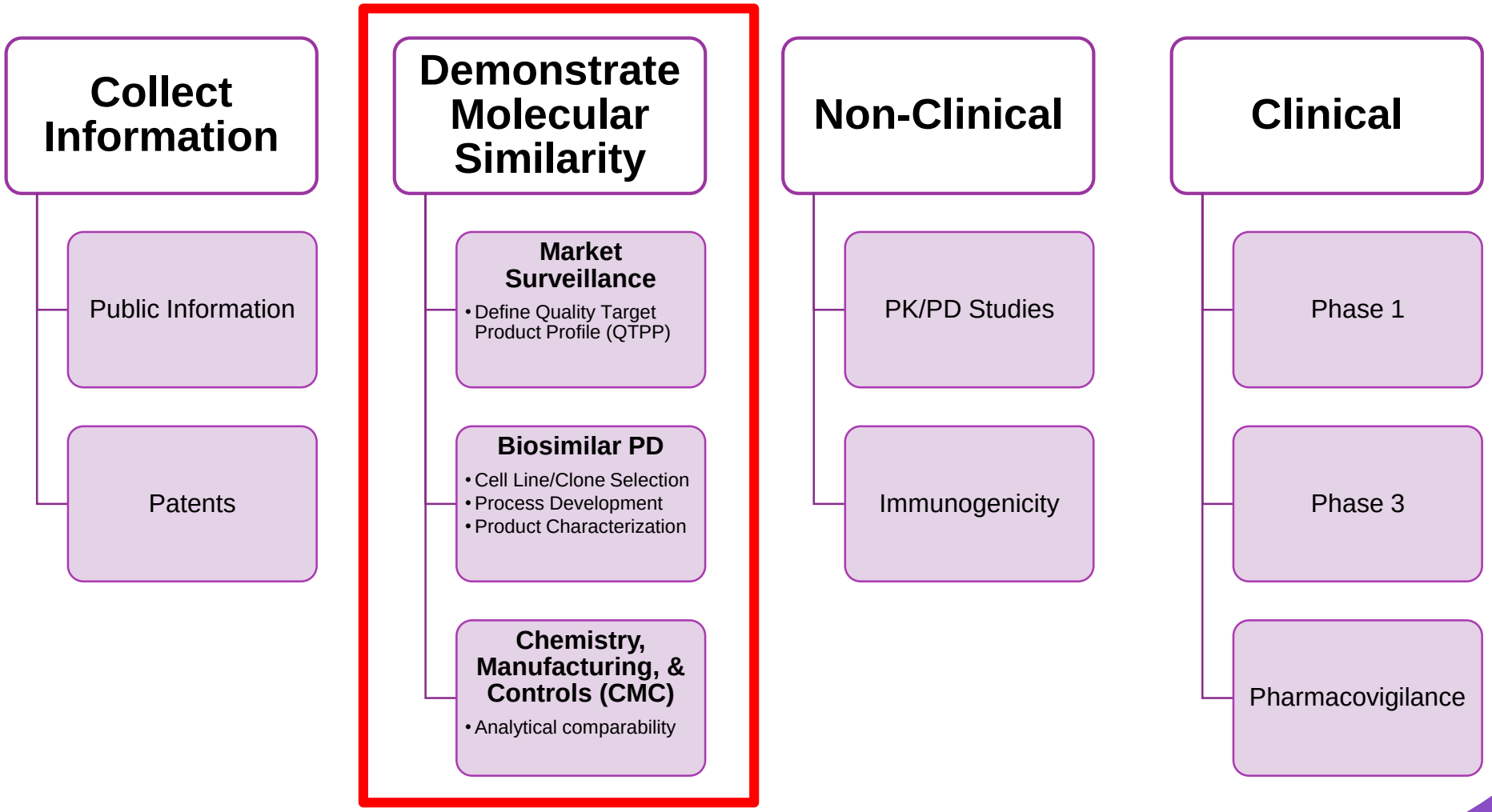
- Goal in this stage = understand the biochemical properties of the reference or innovator product

- Biosimilar developer lacks any proprietary information about the innovator product
  - Development reports, batch records, release specification

- Developer must mine public sources for information
  - Generally can obtain amino-acid (AA) sequence, type of product, mechanism of action, dosage, and formulation
  - Intellectual property laws prevent manufacturers from using innovator production process

Source: Manzi A.E., et al (2018) In: Gutka H., et al. Biosimilars

Biosimilar Development



Source: Manzi A.E., et al (2018) In: Gutka H., et al. Biosimilars

Step 2: Demonstrate Molecular Similarity

First must define the Quality Target Product Profile (QTPP), or the “originator fingerprint”

- Requires molecular analysis of reference product

QTPP is defined as a combination of **Clinical Quality Attributes (CQA’s)**, or physicochemical attributes

- CQA’s must closely match that of reference product to avoid clinically meaningful differences

Source: Manzi A.E., et al (2018) In: Gutka H., et al. Biosimilars

Clinical Quality Attributes for Reverse Engineering

Protein functional aspects

Shed light on MOA & intended biological activity

Structural differences

Post-translational modifications (PTMs), ie glycosylation, deamidation

Protein molecular state

Aggregation versus degradation

Source: Vulto, A.G., et al. *Rheumatology, 56*(suppl_4), iv14–iv29.

Quality Target Product Profile (QTPP)

Category	Quality Attribute	Analytical Method
Identity	Primary sequence of amino acids	Peptide mapping by RP-HPLC/UV
Content	Protein concentration	UV Spectroscopy
Purity	Size Variants	SEC-HPLC with UV detection, capillary electrophoresis
	Charge Variants	Capillary isoelectric focusing, Hydrophobic interaction chromatography
	Glycosylation	Oligosaccharide-mapping/normal phase HPLC with fluorescence detection
Potency	Binding affinity, proliferation	Specific assays
Process-Related Impurities	Residual process impurities	Specific to process
	Residual host cell proteins	Specific to expression system
	Residual host cell DNA	qPCR

Source: Manzi A.E., et al (2018) In: Gutka H., et al. Biosimilars

Cell Line Selection and Engineering

First step in manufacturing process is selection of the cell line

- Cell line is key determinant of glycosylation patterns (impacts PK/PD)

Cell Systems Used:

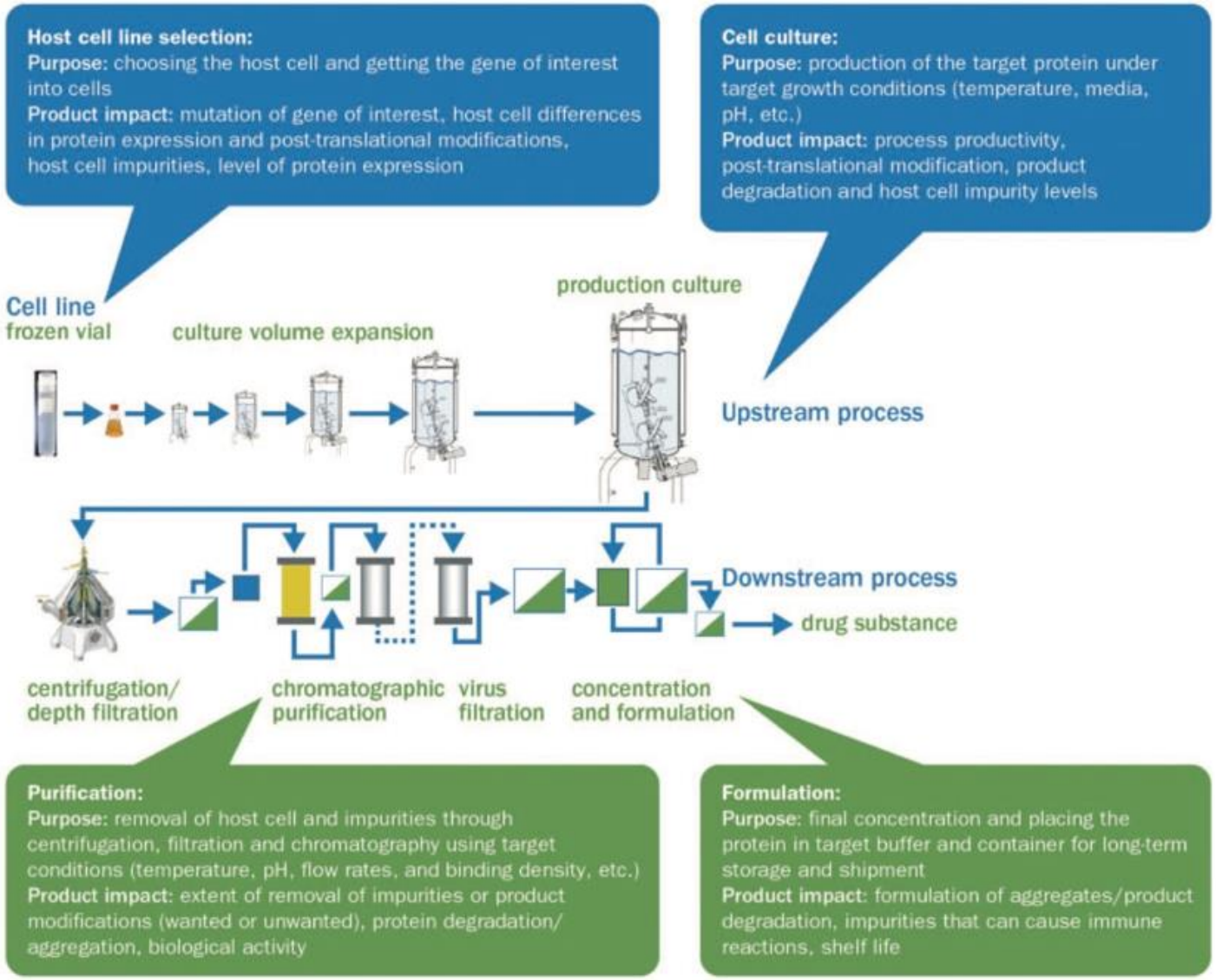
- Yeast
- *Escherichia coli*
- Baculovirus
- Mammalian cells

Chinese Hamster Ovary (CHO) cell lines are common

- Similar glycosylation patterns to humans
- Able to grow in suspension, stable in changing pH
- High specific yield

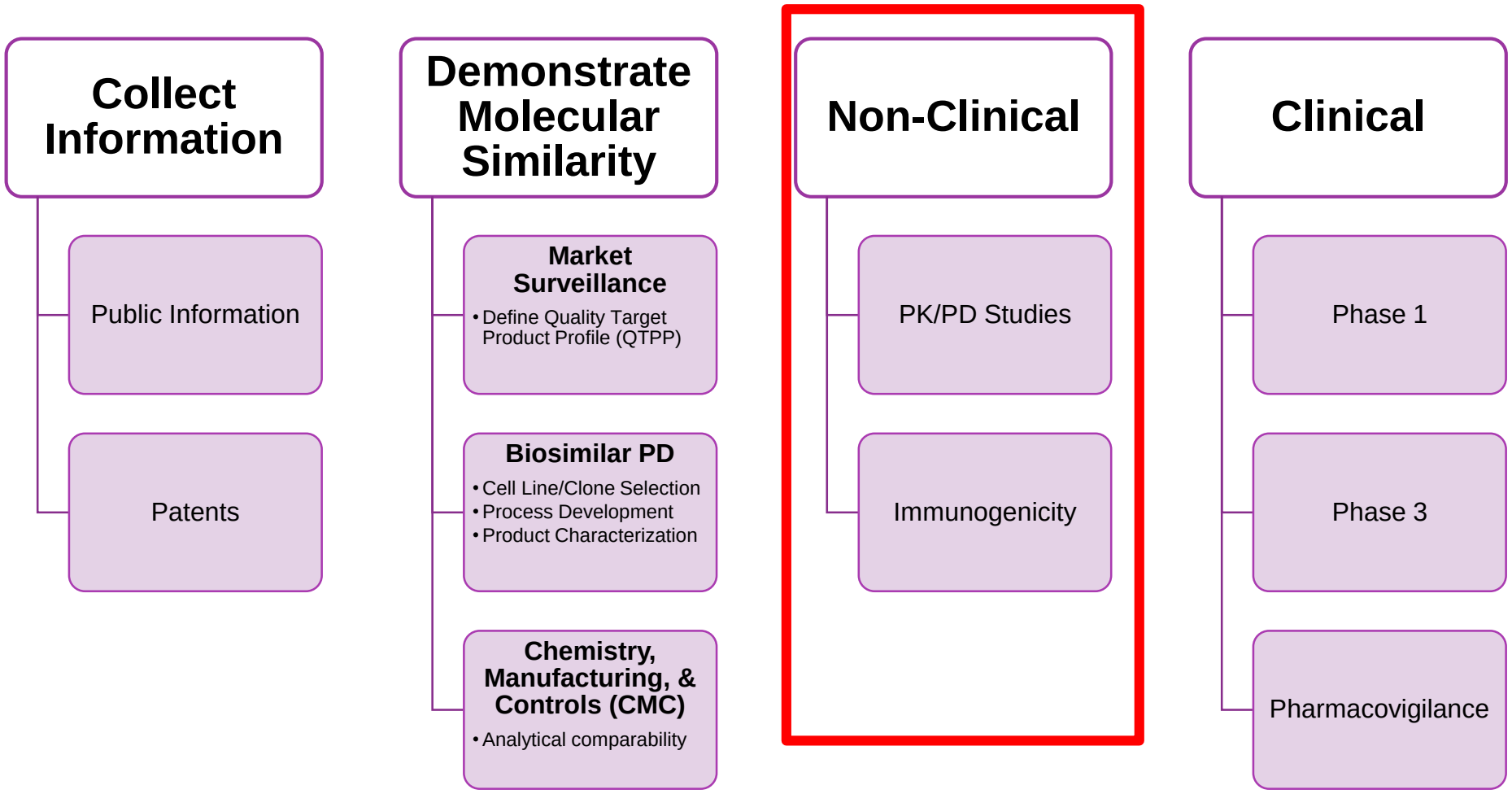
Source: Ahmed, I., et al (2012. *Clin Ther*. *34*(2), 400–419.

Protein Development



Source: Vulto, A. G., et al (2017). *Rheumatology 56* (suppl_4), iv14–iv29.

Biosimilar Development



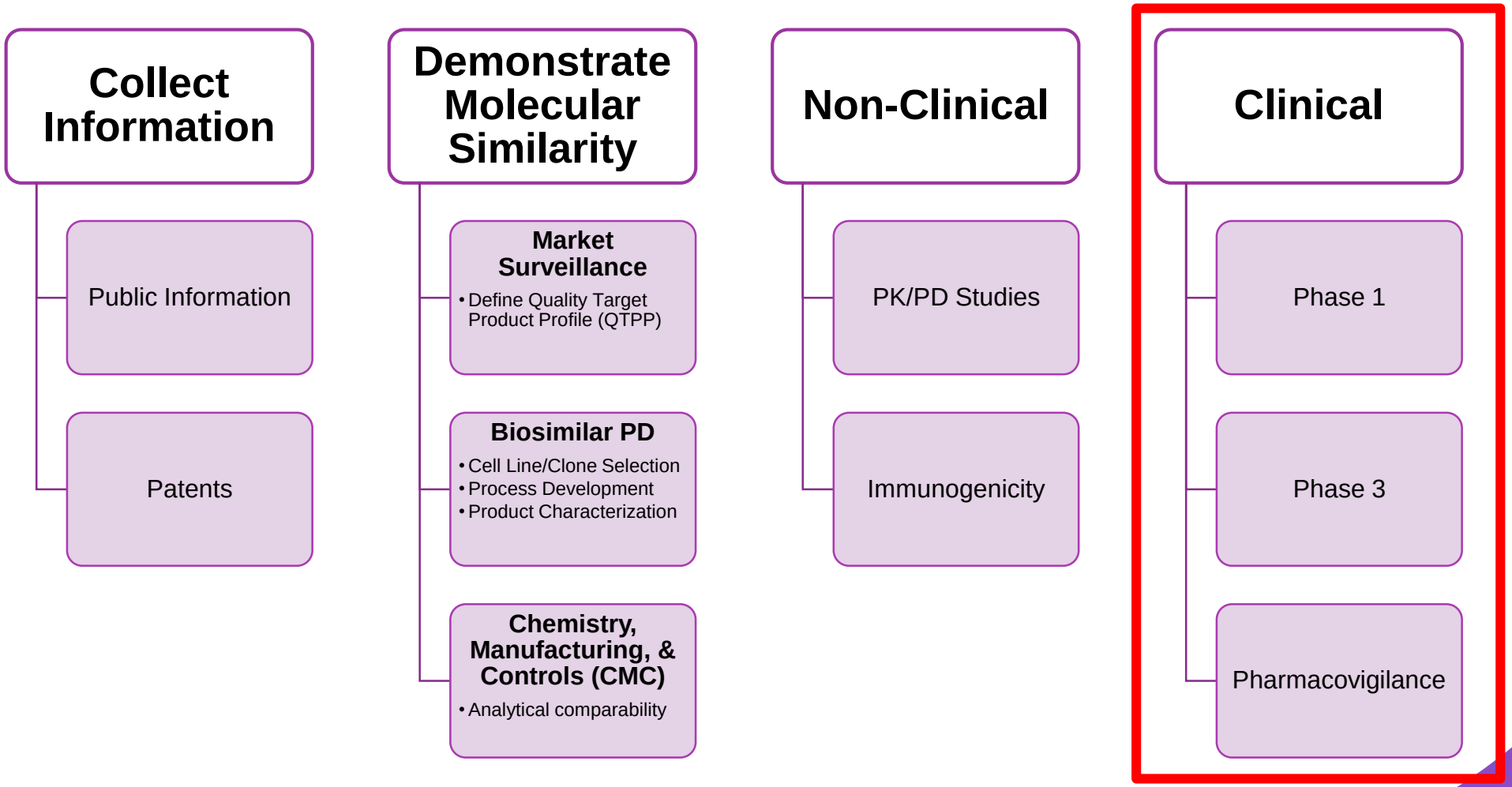
Source: Manzi A.E., et al (2018) In: Gutka H., et al. Biosimilars

Step 3:

Nonclinical PK/PD Studies

- Animal studies
- If in humans, conducted in healthy volunteers
- Pharmacodynamic studies if residual uncertainty after PK studies
- Functional assays performed for detection of immunogenicity

Biosimilar Development



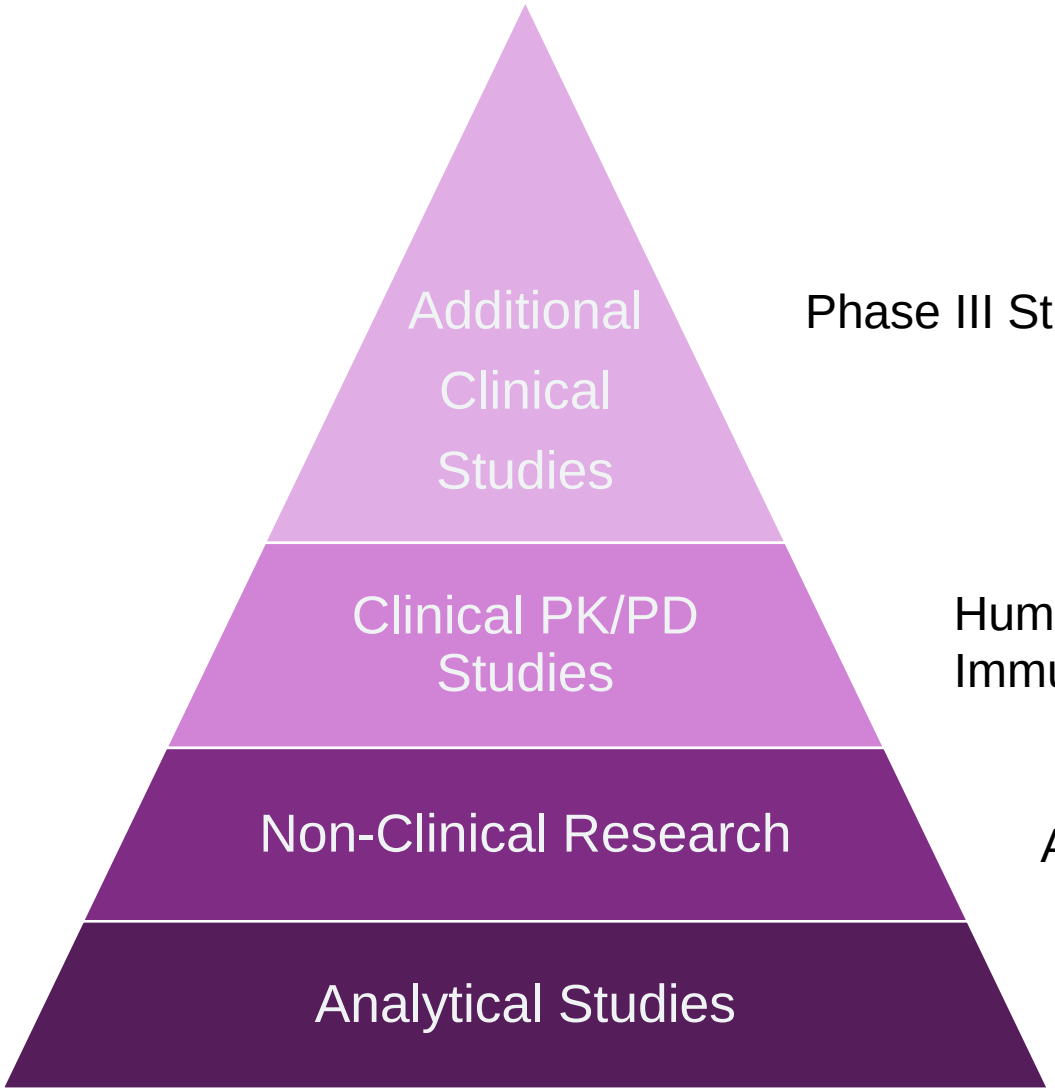
Source: Manzi A.E., et al (2018) In: Gutka H., et al. Biosimilars

Step 4: Clinical Studies

- Phase III clinical trials conducted in patients with indication that is seeking approval
- Additional immunogenicity assessments
- The FDA sets a predetermined margin within which the biosimilar must perform to be approved

Step-Wise Evaluation of Biosimilars

Step-Wise Evaluation of Biosimilars



Phase III Studies

Human PK/PD Studies &
Immunogenicity assessment

Animal Studies

Structural and functional assays

Step-Wise Evaluation of ABP 215, an approved bevacizumab biosimilar

Bevacizumab (Avastin®)

- A recombinant humanized monoclonal immunoglobulin G1 (IgG1) antibody.
- Bevacizumab binds to vascular endothelial growth factor A (VEGF-A) and prevents the binding of VEGF-A to VEGF receptors on the surface of endothelial cells, inhibiting endothelial cell proliferation and new blood vessel formation, thereby leading to normalization of the tumor vasculature.

Source: Ferrara N, et al. Nat Rev Drug Discov. 2004;3(5):391–400.

Approval of ABP 215

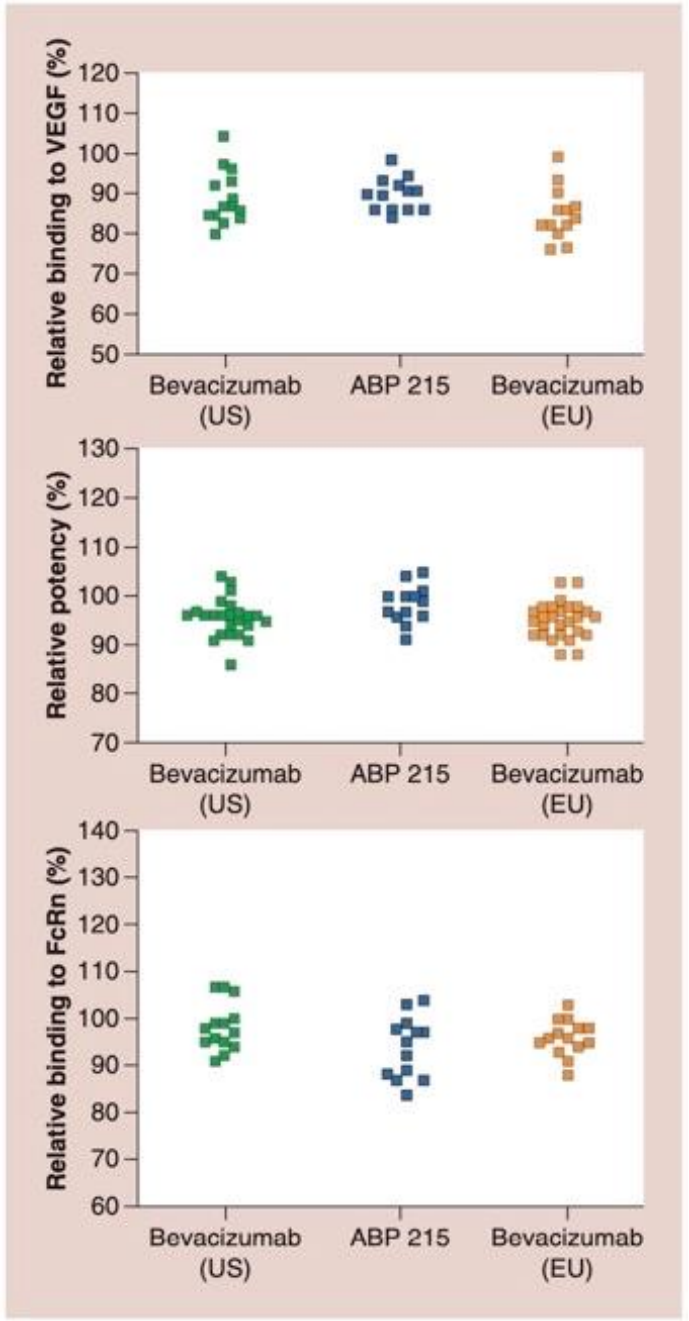
- Bevacizumab-awwb (MVASI®)
- Comparative structural analyses of ABP 215 to bevacizumab RP (Avastin®) demonstrated:
  - Structural similarity
  - Similar particle and aggregate levels
  - Similar degradation rates
  - General properties
  - Biological properties

Analytical Studies

Source: Thomas, M., et al (2019). *Immunotherapy*, *11*(15), 1337–1351.

Functional Studies

- F_c binding characteristics
- Relative potency by proliferation inhibition
- Binding to VEGF



Source: Thomas, M., et al (2019). *Immunotherapy*, *11*(15), 1337–1351.

Approval of ABP 215

- *In vivo* assessments of functional similarity conducted for:
  - Antitumor activity of ABP 215

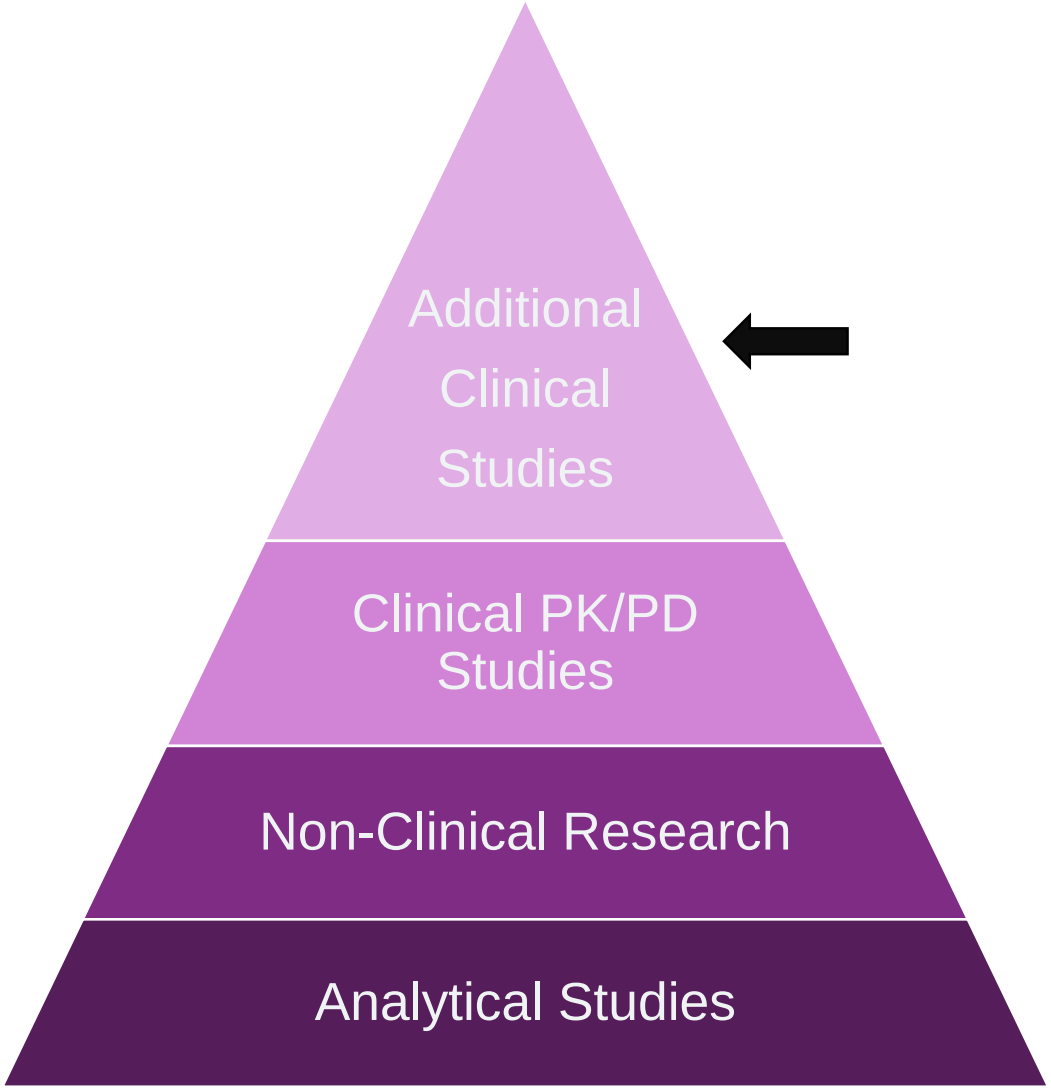
Source: Thomas, M., et al (2019). *Immunotherapy*, *11*(15), 1337–1351.

Approval of ABP 215

- Clinical pharmacokinetic analysis conducted in 202 healthy men
  - Randomized, single-blind 3 arm study; single 3mg/kg IV infusion
  - Primary endpoints:
    - Maximum serum concentration (C_{max})
    - Area Under the Curve (AUC)
    - Treatment emergent adverse events
    - Vital signs
    - Electrocardiograms
    - Incidence of antidrug antibodies

Source: Thomas, M., et al (2019). *Immunotherapy*, *11*(15), 1337–1351.

Approval of ABP 215



- Safety and efficacy evaluated in patients with non-squamous non-small cell lung cancer (NSCLC)- The MAPLE Study

Source: Thomas, M., et al (2019). *Immunotherapy*, *11*(15), 1337–1351.

The MAPLE Study

- Purpose: To confirm similarity of ABP 215 to (bevacizumab RP) in advanced non-squamous non-small cell lung cancer (NSCLC)
- Double-blind, randomized Phase III study
- Patients (N = 642) randomized to 15 mg/kg ABP 215 or bevacizumab RP in combination with paclitaxel & carboplatin for 4 to 6 cycles of treatment
- Primary Endpoints:
  - Risk rate of the Overall Response Rate (ORR) in the ITT population
- Secondary Endpoints:
  - Risk difference of ORR
  - Duration of Response (DOR)
  - Progression Free Survival (PFS)

Source: Thomas, M., et al (2019). *Immunotherapy*, *11*(15), 1337–1351.

MAPLE Study Results

Primary Endpoints:

- In the ITT population, RR of 0.93 [90% CI: 0.80 to 1.09]
  - Prespecified Equivalence Margin of 0.67 to 1.5

Secondary Endpoints:

- Risk Difference of ORR - 2.9% [90% CI: -9.26 to 3.45%]
- Duration of Response (DOR); Median 5.8 months [95% CI: 4.9 to 7.7] for ABP 215, 5.6 months [95% CI: 5.1 to 6.3] for bevacizumab RP
- Hazard ratio of PFS of 1.03 [90% CI: 0.83 to 1.29]

Safety:

- Serious AE frequency similar between groups
  - ABP 215: 26.2%
  - Bevacizumab RP: 23.3%

Source: Thomas, M., et al (2019). *Immunotherapy*, *11*(15), 1337–1351.

Totality of Evidence (TOE)

- TOE provides scientific justification for extrapolation across approved indications

- In the U.S., bevacizumab-awwb (Mvasi®) is currently approved for:
  - First line treatment of advanced, recurrent, or metastatic NSCLC
  - First or second-line treatment of metastatic colorectal cancer
  - Metastatic renal cell carcinoma
  - Recurrent or persistent cervical cancer
  - Recurrent glioblastoma

Source: Thomas, M., et al (2019). *Immunotherapy*, *11*(15), 1337–1351.

Extrapolation

- Extrapolation across indications refers to the Totality of Evidence (TOE)
- Extrapolation is not a given; must have scientific justification for mechanism of action, pharmacokinetics, immunogenicity
- This is unique to biosimilars
- Approval for all indications for which reference product (RP) is approved
  - May be exceptions in orphan disease states

Source: Thomas, M., et al (2019). *Immunotherapy*, *11*(15), 1337–1351.

BPCI Act and Interchangeability

- The Biologics Price Competition and Innovation Act also established additional requirements for interchangeability
  - Additional standards described in Section 351(k)(4) of Public Health Service Act
- **Interchangeability** is defined by the FDA as a ‘biological product that may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.
- Currently no biosimilars have been designated as “interchangeable”
- High cost associated with additional studies

Source: FDA Guidance For Industry, 2019

Interchangeability Studies

Guidance for Industry

The FDA *recommends* that biosimilars seeking interchangeability should do so for all reference indications

Post-marketing data not sufficient for interchangeability designation; however, can be helpful in determining what data is necessary for determining interchangeability

Requirements

- Switching studies with two or more alternate exposures/switch intervals
- Study population should be adequately sensitive

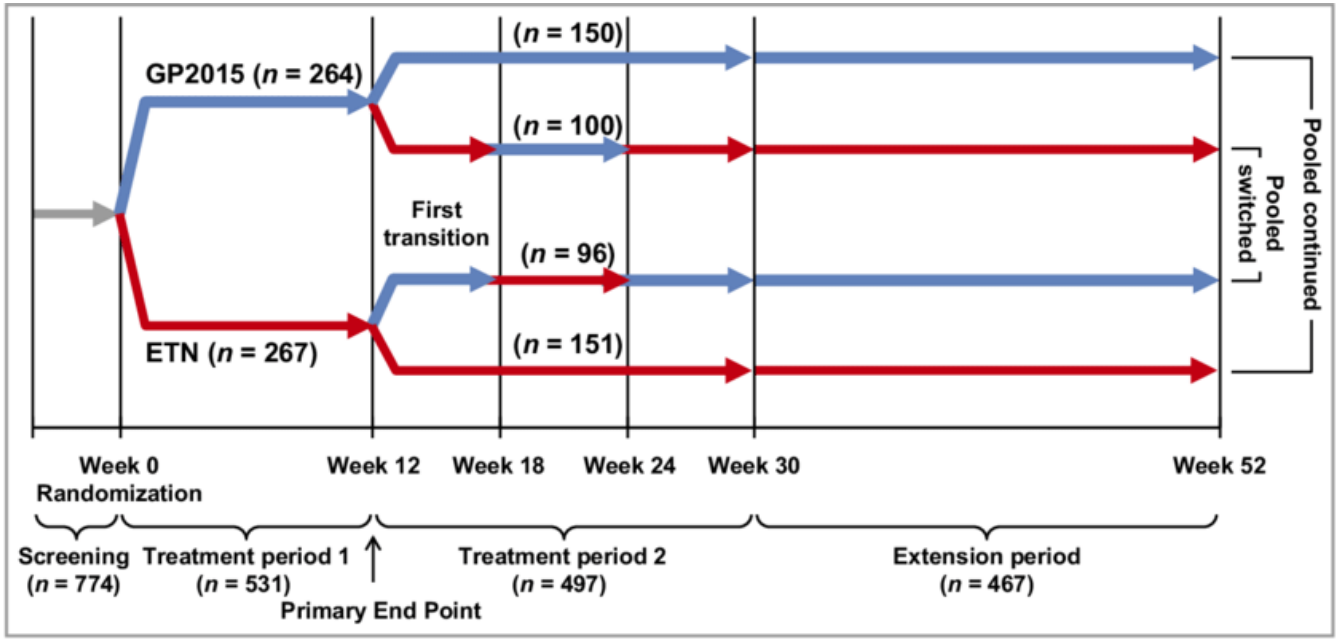
Endpoint Assessments

- Clinical PK/PD endpoints & immunogenicity sampling after final switch
  - Most likely to be sensitive to changes in exposure and/or activity versus clinical endpoints

Source: FDA Guidance For Industry, 2019

Interchangeability

The EGALITY study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis.



GP2015 = Etanercept biosimilar; ETN = Etanercept

Source: Griffiths C, et al. Br J Dermatol. 2017;176(4):928-38. Figure 1; p. 930.

Pharmacovigilance Efforts

Biosimilar Nomenclature

- Under the Public Health Service Act (PHS), biological products will bear a *nonproprietary name* with an FDA-designated suffix
  - The nonproprietary name will be a proper name that is a combination of the **core name** and a **distinguishing suffix** that is devoid of meaning and composed of 4 lowercase letters
  - Examples: Rituximab-arrx, infliximab-axxq

- Aids in accurate product identification for pharmacovigilance efforts
  - Proprietary names and NDCs can change over time

Source: FDA Guidance For Industry, 2019

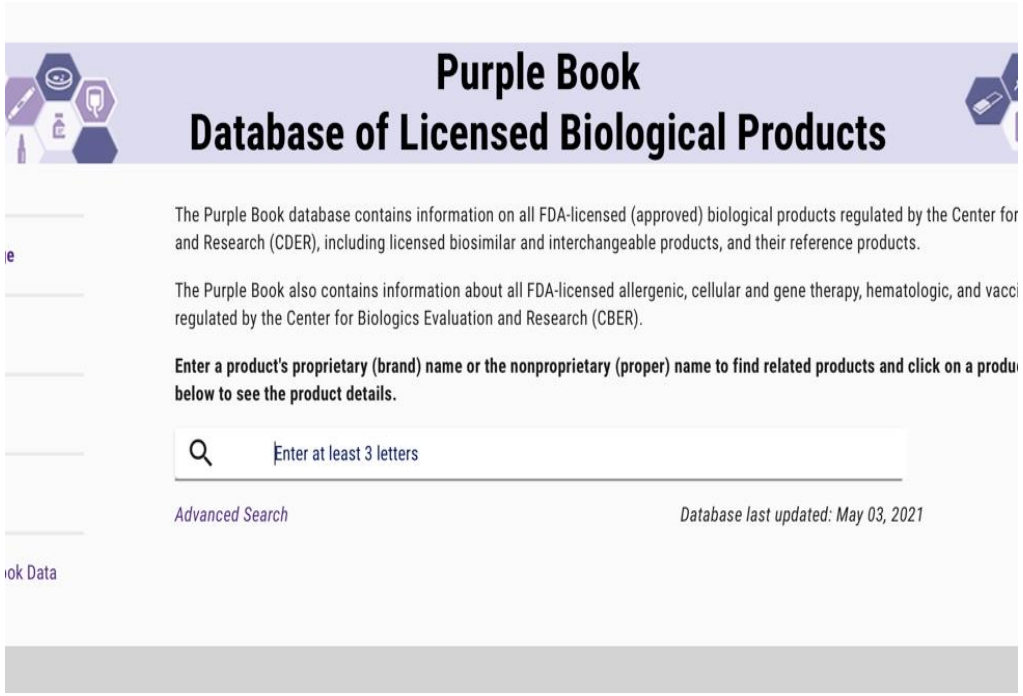
The Pharmacist’s Role in Biosimilar Pharmacovigilance

- Pharmacovigilance programs are essential for recognizing and mitigating the risks associated with the use of biosimilar agents
- Pharmacists must prioritize use of the MedWatch FDA Adverse Event Reporting System (FAERS) in order to alert the FDA of serious adverse reactions to products, as well as reduce the risk of medication errors
- Information that should be reported to MedWatch:
  - **Unexpected side effects or adverse events**
  - **Product quality problems**
  - **Product Use/Medication Errors that can be prevented**
  - **Therapeutic failures**

Source: U.S. Food and Drug Administration. 2021

The Purple Book

- In February 2020, the FDA launched a searchable, online database of biological products
- Accessible at: https://purplebooksearch.fda.gov
- Continually updated, products added within 10 days of approval



Drug Approval Package: Mvasi (bevacizumab-awwb)

Company: Amgen Inc.
Application Number: 761028
Approval Date: 09/14/2017

Drugs@FDA information available about Mvasi

Persons with disabilities having problems accessing the PDF files below may call (301) 796-3634 for assistance.

FDA Approval Letter and Labeling

- Approval Letter(s) (PDF)
- Printed Labeling (PDF)

FDA Application Review Files

- Summary Review (PDF)
- Officer/Employee List (PDF)
- Cross Discipline Team Leader Review (PDF)
- Medical Review(s) (PDF)
- Chemistry Review(s) (PDF)
- Pharmacology Review(s) (PDF)

APPLICATION NUMBER:

761028Orig1s000

Trade Name:	Mvasi Injection, 100 mg/4 mL and 400 mg/16 mL
Generic or Established:	bevacizumab-awwb
Sponsor:	Amgen Inc.
Approval Date:	September 14, 2017
Indication:	Mvasi is indicated for: · The treatment of patients with metastatic colorectal cancer, with intravenous 5 fluorouracil–based chemotherapy for first or second line treatment. · The treatment of patients with metastatic colorectal cancer, with fluoropyrimidine irinotecan or fluoropyrimidine oxaliplatin based chemotherapy for second line treatment in patients who have progressed on a first line bevacizumab product-containing regimen. · Patients with non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease. · The treatment of glioblastoma, as a single agent for adult patients with progressive disease following prior therapy. · The treatment of patients with metastatic renal cell carcinoma with interferon alfa.

Assessment Questions

Pharmacist & Nurse Question 1

Immunogenicity does NOT increase with:

A) Small-molecule generic drugs

B) Proportion of aggregated and deaggregated proteins

C) Process-related impurities

D) Route of administration

Question 1: Correct Response

Immunogenicity does NOT increase with:

A) Small-molecule generic drugs

B) Proportion of aggregated and deaggregated proteins

C) Process-related impurities

D) Route of administration

Pharmacist & Nurse Question 2

The regulatory process of biosimilar products requires the following data: animal studies, human PK/PD data, head-to-head clinical trials, and:

A) Switching studies

B) Comparative structural analyses

C) A REMS program

D) No additional studies are necessary

Question 2: Correct Response

The regulatory process of biosimilar products requires the following data: animal studies, human PK/PD data, head-to-head clinical trials, and:

A) Switching studies

B) **Comparative structural analyses**

C) A REMS program

D) No additional studies are necessary

Pharmacist & Nurse Question 3

According to the most recent guidance by the FDA for pharmacovigilance of biosimilars, which of the unique identifiers should be added to the non-proprietary name?

A) An asterisk

B) NDC number

C) A four-letter suffix, devoid of meaning

D) Molecular name

Question 3: Correct Response

According to the most recent guidance by the FDA for pharmacovigilance of biosimilars, which of the unique identifiers should be added to the non-proprietary name?

A) An asterisk

B) NDC number

C) A four-letter suffix, devoid of meaning

D) Molecular name

Pharmacy Technician Question 1

Of the below options, which is NOT characteristic of biosimilar agents?

A) Cost of development between $100-250 million per agent

B) Reference Guide is the Orange Book

C) Large, complex protein structure

D) Analytical, animal, & clinical studies required for approval

Question 1: Correct Response

Of the below options, which is NOT characteristic of biosimilar agents?

A) Cost of development between $100-250 million per agent

B) Reference Guide is the Orange Book

C) Large, complex protein structure

D) Analytical, animal, & clinical studies required for approval

Pharmacy Technician Question 2

True or False?

The manufacturing of biosimilars requires Clinical Quality Attributes (CQA’s) to be defined for maximum safety and efficacy of the product.

Question 2: Correct Response

True or False?

The manufacturing of biosimilars requires Clinical Quality Attributes (CQA's) to be defined for maximum safety and efficacy of the product. There can be dozens of these for each molecular product. The FDA does not set a specific regulatory standard for each characteristic but does provide recommendations on statistical approaches when evaluating analytical similarity.

Pharmacy Technician Question 3

True or False?

All biosimilar agents are considered interchangeable with their reference product.

Question 3: Correct Response

True or False

Biosimilar agents are NOT considered interchangeable with the reference product unless designated as such in the Purple Book. The designation as interchangeable requires additional clinical ‘switching’ studies to confirm that immunogenicity does not develop when switching between agents.

References

1) Zelenetz AD, Ahmed I, Braud EL et al. NCCN biosimilars white paper: regulatory, scientific, and patient safety perspectives. *J Natl Compr Canc Netw. 2011; 9(suppl 4):S1-22.*

2) Crommelin, Daan & Bermejo, T. & Bissig, M.. (2005). Pharmaceutical evaluation of biosimilars: Important differences from generic low-molecular-weight pharmaceuticals. Eur J Hosp Pharm Sci. 11. 11-17.

3) U.S. Food and Drug Administration. Biosimilar Development, Review, and Approval; 2017. https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval

4) Allan Coukell, "Specialty Drugs and Health Care Costs," Pew Charitable Trusts, Drug Spending Research Initiative, November 16, 2015. As of September 27, 2017: http://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2015/11/specialty-drugs-and-health-care-costs

5) National Pharmaceutical Services, "Specialty Drug Spending," white paper, undated. As of September 27, 2017: https://www.pti-nps.com/nps/wp-content/uploads/2017/04/NPS_Specialty-Medication-White-Paper-Web.pdf

6) Mulcahy, A. W., Hlavka, J. P., & Case, S. R. (2018). Biosimilar Cost Savings in the United States: Initial Experience and Future Potential. *Rand health quarterly*, *7*(4), 3.

7) Manzi A.E., Ultee M.E. (2018) Biosimilars Drug Substance Development and Manufacturing: Effective CMC Strategy. In: Gutka H., Yang H., Kakar S. (eds) Biosimilars. AAPS Advances in the Pharmaceutical Sciences Series, vol 34. Springer, Cham.

8) ASHP Advantage Media. A Health System Pharmacist's Guide to Biosimilars: Regulatory, Scientific, and Practical Considerations. 2013.

9) U.S. Department of Health and Human Services. Labeling for Biosimilar Products. Guidance for Industry (2018). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/labeling-biosimilar-products-guidance-industry

10) Thomas, M., Thatcher, N., Goldschmidt, J., Ohe, Y., McBride, H. J., & Hanes, V. (2019). Totality of evidence in the development of ABP 215, an approved bevacizumab biosimilar. *Immunotherapy*, *11*(15), 1337–1351.

11) Coggio B.D., Vogel R., Francis T. (2018) Litigation-Related Issues Under the Biologics Price Competition and Innovation Act. In: Gutka H., Yang H., Kakar S. (eds) Biosimilars. AAPS Advances in the Pharmaceutical Sciences Series, vol 34. Springer, Cham.

12) Schellekens H., Lietzan E., Faccin F., Venema J. Biosimilar Monoclonal Antibodies: The Scientific Basis for Extrapolation. *Expert Opin. Biol. Ther.* 2015;15:1633–1646

13) Trukhin, D., et al. 2021. Efficacy, Safety and Immunogenicity of MB02 (Bevacizumab Biosimilar) versus Reference Bevacizumab in Advanced Non-Small Cell Lung Cancer: A Randomized, Double-Blind, Phase III Study (STELLA). *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy*, 10.1007/s40259-021-00483-w. Advance online publication.

14) Li, E., Ramanan, S., & Green, L. (2015). Pharmacist Substitution of Biological Products: Issues and Considerations. *Journal of managed care & specialty pharmacy*, *21*(7), 532–539.

15) Tbo-filgrastim prescribing information. North Wales, PA: Teva Pharmaceuticals USA; 2012 Aug. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125294Orig1s000SumR.pdf

16) U.S. Food and Drug Administration. Medwatch. 2021. Accessed at: https://www.accessdata.fda.gov/scripts/medwatch/

17) Ahmed, I., Kaspar, B., & Sharma, U. (2012). Biosimilars: impact of biologic product life cycle and European experience on the regulatory trajectory in the United States. *Clinical therapeutics*, *34*(2), 400–419.

18) Vulto, A. G., & Jaquez, O. A. (2017). The process defines the product: what really matters in biosimilar design and production?. *Rheumatology (Oxford, England)*, *56*(suppl_4), iv14–iv29.

19) Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov. 2004;3(5):391–400. doi:10.1038/nrd1381.

20) Araújo, F. C., Gonçalves, J., & Fonseca, J. E. (2016). Pharmacoeconomics of Biosimilars: What Is There to Gain from Them?. *Current rheumatology reports*, *18*(8), 50.

21) Kang, H. N., Thorpe, R., Knezevic, I., & Survey participants from 19 countries (2020). The regulatory landscape of biosimilars: WHO efforts and progress made from 2009 to 2019. *Biologicals : journal of the International Association of Biological Standardization*, *65*, 1–9.

22) Raedler L. A. (2016). Zarxio (Filgrastim-sndz): First Biosimilar Approved in the United States. *American health & drug benefits*, *9*(Spec Feature), 150–154.

23) Griffiths, C., Thaçi, D., Gerdes, S., Arenberger, P., Pulka, G., Kingo, K., Weglowska, J., EGALITY study group, Hattebuhr, N., Poetzl, J., Woehling, H., Wuerth, G., & Afonso, M. (2017). The EGALITY study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis.

Thank you!!

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