THE BIOSIMILAR DEVELOPMENT PATHWAY AND CHALLENGES OF PRACTICAL INTEGRATION

ROBIN LOCKHORST PHARM.D., BCPS, BCOP

DISCLOSURES

- None

HISTORY

- Developed in response to questions about the biosimilar development process and potential impact on research at the February 2019 Semi-annual NRG meeting
  - NRG is the NCI Cooperative Group that ACI is a member of
- Presented at the July 2019 Semi-annual NRG meeting
  - Medical Oncology Pharmacy Subcommittee Meeting
    - Full presentation
  - Medical Oncology Workshop
    - Abbreviated presentation
- Expanded this presentation since time allowed

OBJECTIVES

- Contrast the generic and biosimilar medication development pathways
- Outline the biosimilar research requirements for FDA approval
- Identify practical challenges of biosimilar use including interchangeability, formulary restrictions, prescribing, dispensing, and research

BIOSIMILARS ARE ALL OVER THE NEWS!

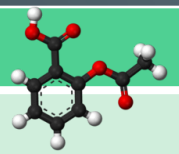
- FDA approved the 1st biosimilar in March 2015
  - 23 approved as of August 2019
    - 5 supportive oncology
    - 9 therapeutic oncology
- What is a biosimilar & how does it differ from a generic?

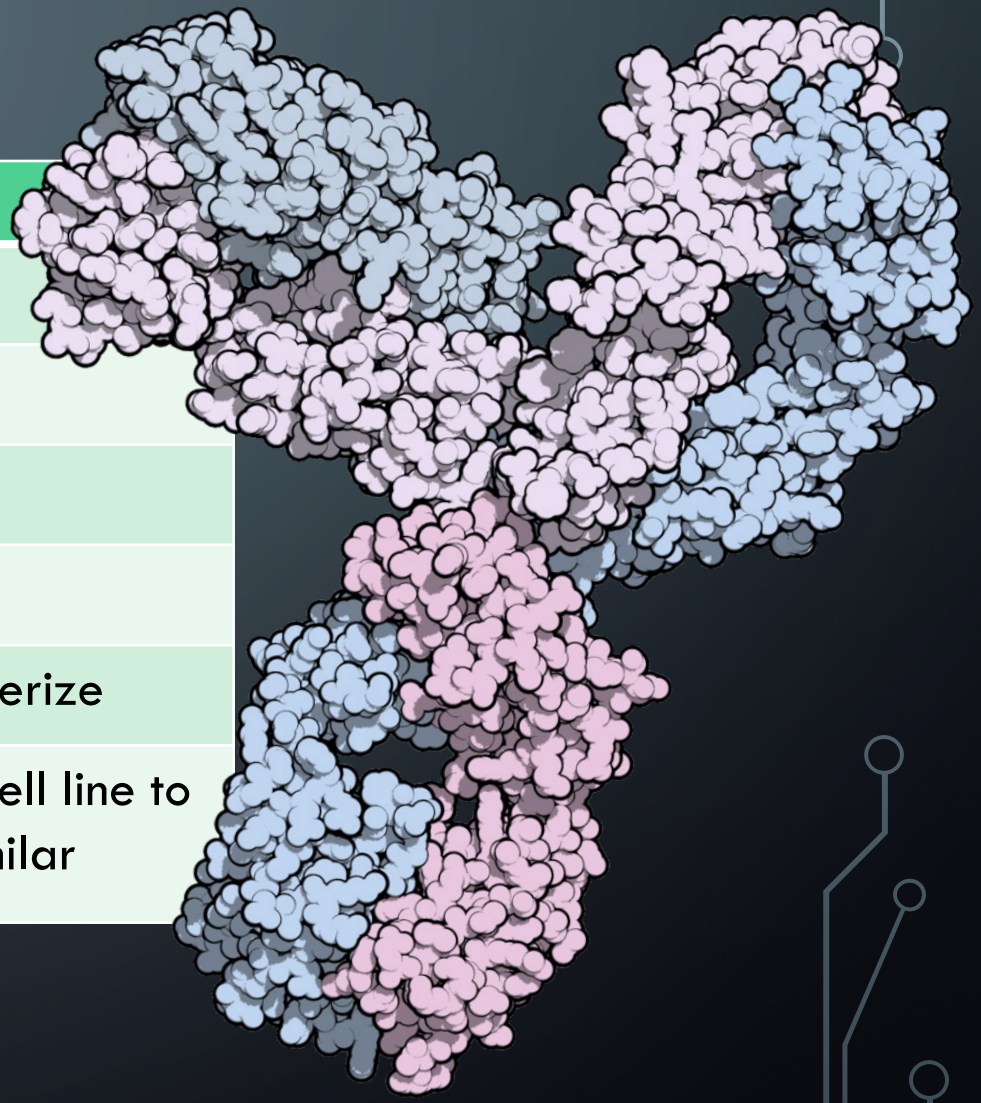
Biosimilar Product Information. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information.
Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability. Evaluations. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information.

WHAT IS THE DIFFERENCE?

Small Molecule	Biologic
Copy	“Attempted Copy”
Generic	Biosimilar

WHAT IS THE DIFFERENCE?

Small Molecule 	Biologic
Low molecular weight	High molecular weight
Chemical synthesis	Living cell cultures
Non-immunogenic	Immunogenic
Simple, well-defined structure	Complex structure
Able to analytically characterize	Impossible to fully characterize
Chemically manufactured identical copy → Generic	Manufactured in a living cell line to be highly similar → Biosimilar



Declerck, PJ. Biologicals and biosimilars: a review of the science and its implications. GaBI Journal. 2012.

BIOLOGICS MANUFACTURING PROCESS

- Formal process changes must be reported to the FDA
  - Changes at any stage: cell source, purification techniques, storage
  - Demonstrate that the product has been maintained within a preset specification limit so as not to affect safety & efficacy
- Regulations derived from International Quality Guidelines (ICH Q5E)
  - Pre- & post-change product must be "highly similar"
- Highly similar lots of biologics are on the market at the same time & used interchangeably in practice
- Demonstrates complexity of biologic products & the basis of the biosimilar definition

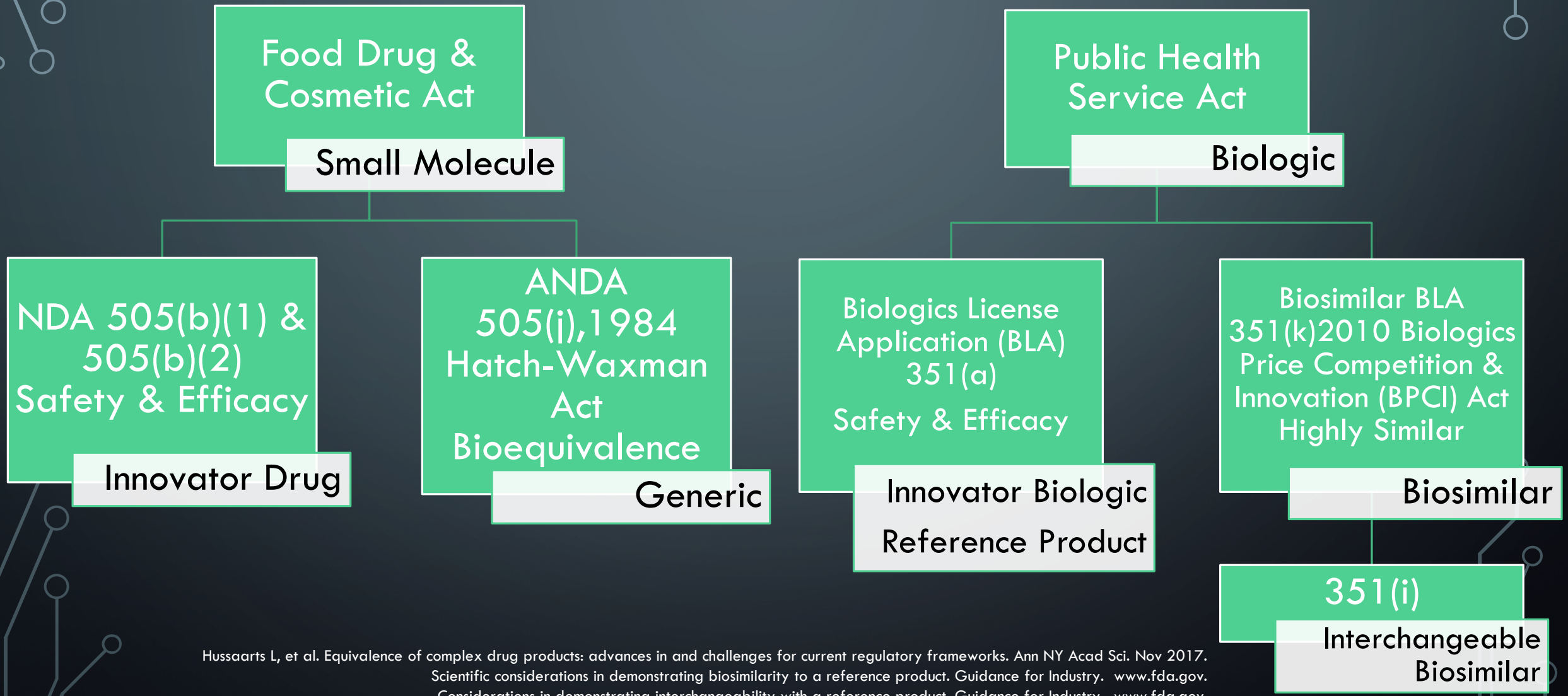
Declerck, PJ. Biologicals and biosimilars: a review of the science and its implications. GaBI Journal. 2012.
Q5E Comparability of biotechnological/biological products subject to changes in their manufacturing process. Guidance for Industry. 2005. www.fda.gov.
Kozlowski S, et al. Developing the nation's biosimilars program. N Engl J Med. Aug 4, 2011.
Schiestl M, et al. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nature Biotechnology. April 2011.

WHAT IS THE FDA DEFINITION OF A BIOSIMILAR?

- Biosimilar
  - "biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components," and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product"
- Companies are attempting to reproduce biologics with expired patents
  - Biosimilar definition replaced the unofficial term "follow-on biologics"
- FDA created a new approval pathway with the definition

Biosimilars action plan: balancing innovation and competition. July 2018. www.fda.gov.
Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for Industry. www.fda.gov.
McCamish M, et al. The state of the art in the development of biosimilars. Clinical Pharmacolog & Therapeutics. March 2012.
Kozlowski S, et al. Developing the nation's biosimilars program. N Engl J Med. Aug 4, 2011.

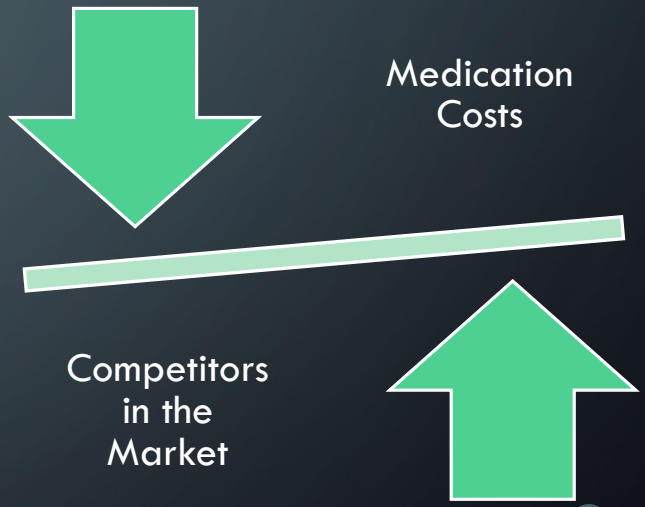
FDA APPROVAL PATHWAYS



Hussaarts L, et al. Equivalence of complex drug products: advances in and challenges for current regulatory frameworks. Ann NY Acad Sci. Nov 2017.
Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for Industry. www.fda.gov.
Considerations in demonstrating interchangeability with a reference product. Guidance for Industry. www.fda.gov.

FDA APPROVAL PATHWAYS: MARKET COMPETITION

- Generic approval pathway allows for cost savings
  - Bioequivalence didn't require reproduction of costly clinical trials
- Competition produces cost savings & improved access
  - Biosimilar pathway was approved to promote competition & affordability
- Biosimilar cost savings?
  - Prescription database study 2016 → 2017 G-CSF expenditures decreased by 10.9% in 9 sectors including clinics & nonfederal hospitals
    - 3 products available: 2 biologic G-CSF + 1 biosimilar
  - Research & development costs high with complex manufacturing



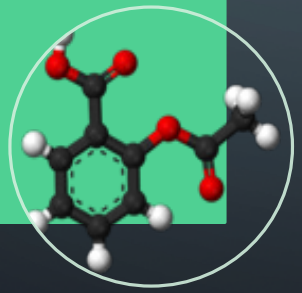
Biosimilars action plan: balancing innovation and competition. July 2018. www.fda.gov.
Schumock GT, et al. National trends in prescription drug expenditures and projections for 2018. Am J Health-Syst Pharm. 2018.
Hornecker, JR. Generic drugs: history, approval process, and current challenges. U.S. Pharmacist. June 18, 2009.

RESEARCH REQUIREMENTS

- Bioequivalence
  Same extent/rate absorption & availability
  - Cmax/AUC
- Pharmaceutical Equivalence
  Active ingredients, dosage form, route of administration, strength

Generic

Therapeutic Equivalence: expected to produce same clinical effect & safety profile



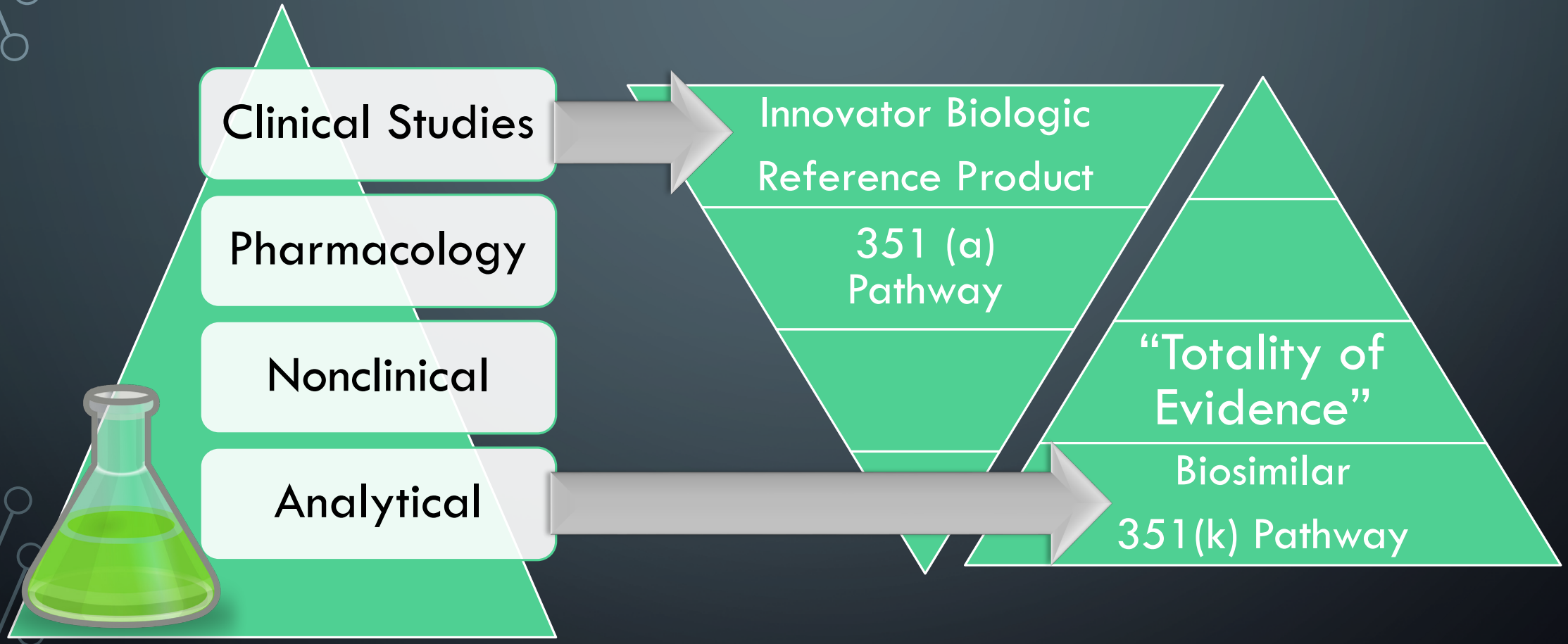
- Analytical & Nonclinical Function Similarity
  Same MOA, dosage form, route, strength
- Pharmacological Similarity
  PK/PD
- Clinical Similarity
  Clinical studies in efficacy (+/-), immunogenicity, safety

Biosimilar

Highly Similar

Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for Industry. www.fda.gov.
Considerations in demonstrating interchangeability with a reference product. Guidance for Industry. www.fda.gov.
Li, E, et al. Pharmacist substitution of biological products: issues and considerations. JMCP. July 2015.
Hornecker, JR. Generic drugs: history, approval process, and current challenges. U.S. Pharmacist. June 18, 2009.

RESEARCH REQUIREMENTS



Declerck, PJ. Biologicals and biosimilars: a review of the science and its implications. GaBI Journal. 2012.

DEVELOPMENT OF A BIOSIMILAR APPLICATION

- Reverse engineer the reference product and determine the lot-to-lot variability
  - Biosimilar is then developed to fall within this threshold of variation
- Analytical: comparative analytics using advanced technology
  - Structure
    - Identical primary AA sequence & higher order structure
      - Identifying side chain variations
  - Characterize the purity & potency
- Nonclinical: biological function testing
  - To identify if variations in the biosimilar product will affect function
  - In-vitro, in-vivo functional assays, and animal models

Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for Industry. www.fda.gov.
Declerck, PJ. Biologicals and biosimilars: a review of the science and its implications. GaBI Journal. 2012.
McCamish M, et al. The state of the art in the development of biosimilars. Clinical Pharmacolog & Therapeutics. March 2012.

DEVELOPMENT OF A BIOSIMILAR APPLICATION

- Pharmacology: pharmacokinetic/pharmacodynamic studies
  - Testing required because can't predict from analytical/nonclinical data
- Clinical Studies:
  - Immunogenicity assessment required
    - Assess the incidence/severity human immune response: anaphylaxis or neutralizing antibodies
  - Comparative clinical study: reference product vs. biosimilar
    - Goal: identify if any clinically meaningful differences in safety, toxicity, & efficacy
    - May be deemed unnecessary by FDA
    - Most relevant & sensitive study population
    - Equivalence design to demonstrate the biosimilar does not cross an inferiority or superiority margin

McCamish M, et al. The state of the art in the development of biosimilars. Clinical Pharmacolog & Therapeutics. March 2012.

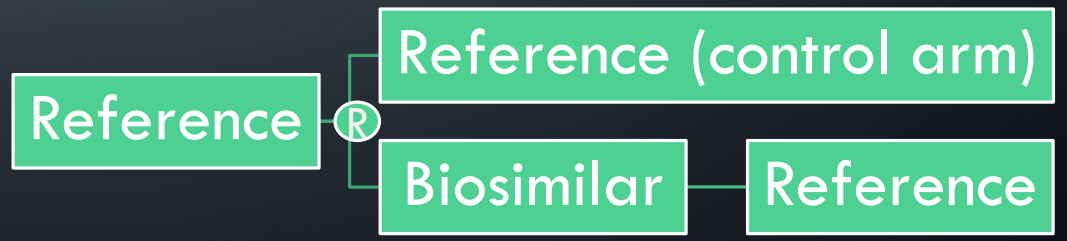
DEVELOPMENT OF A BIOSIMILAR APPLICATION

- Biosimilar Application: review of the "Totality of Evidence"
  - Must meet definition of "highly similar" to be approved
  - Extrapolation: All reference product indications may be approved even if not studied
    - Scientific justification that all indications use the same MOA & show that the PK/PD, immunogenicity, and toxicity would be similar across the treatment populations
- Naming Convention: Biosimilar-kdst
  - Unique random lower-case 4-letter suffix after the non-proprietary name
    - Clearly distinguish what is prescribed, dispensed, administered
    - Useful in adverse event reporting

Li, E, et al. Pharmacist substitution of biological products: issues and considerations. JMCP. July 2015.
Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for Industry. www.fda.gov
Declerck, PJ. Biologicals and biosimilars: a review of the science and its implications. GaBI Journal. 2012
McCamish M, et al. The state of the art in the development of biosimilars. Clinical Pharmacolog & Therapeutics. March 2012

INTERCHANGEABLE BIOSIMILAR DEFINITION

- Meets the definition of a biosimilar AND
- "Can be expected to produce the same clinical result as the reference product in any given patient" AND
- For products administered more than once:
  - Demonstrate no additional risks and no diminished efficacy when switching between reference product and biosimilar
    - Switching study designs
      - Evaluations of PK/PD, immunogenicity, and safety after at least 3 switches



Considerations in demonstrating interchangeability with a reference product. Guidance for Industry. www.fda.gov.

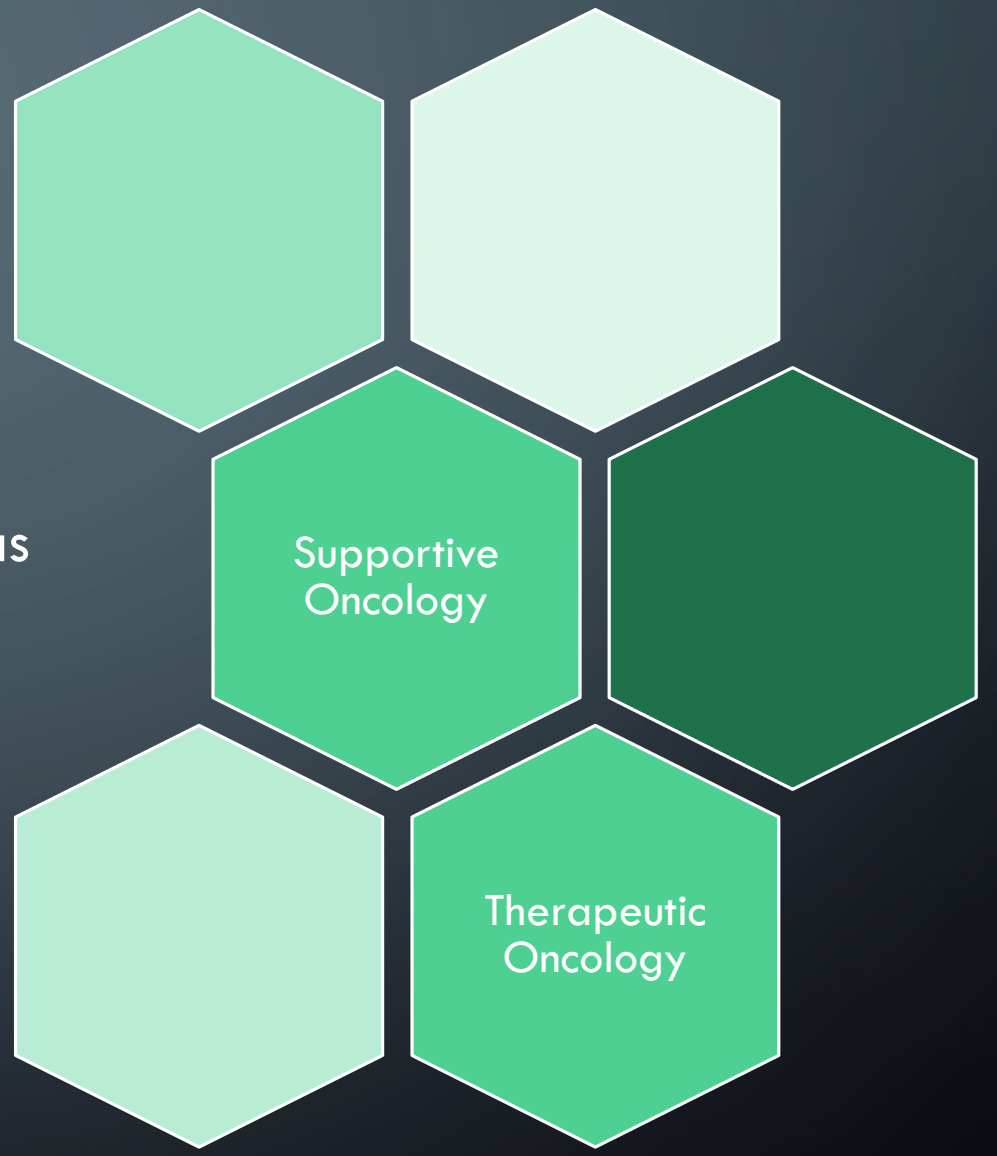
INTERCHANGEABLE BIOSIMILARS

- Purple book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations
- Can be substituted for the reference product without discussing with the provider
  - Actual substitution is up to state legislation which regulates pharmacy practice
  - Oncologists have expressed concern over dispensing a different product than what was written for
  - Pharmacy organizations are promoting communication with providers regarding interchangeable biosimilars
- Important note: biosimilars are not interchangeable with each other!

Considerations in demonstrating interchangeability with a reference product. Guidance for Industry. www.fda.gov.
Cook JW, et al. Academic oncology clinicians' understanding of biosimilars and information needed before prescribing. Ther Adv Med Oncol. 2019
Li, E, et al. Pharmacist substitution of biological products: issues and considerations. JMCP. July 2015.
Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. https://www.fda.gov/drugs/biosimilars/biosimilar-product-

CURRENTLY APPROVED ONCOLOGY BIOSIMILARS

- None are currently approved as interchangeable



SUPPORTIVE ONCOLOGY BIOSIMILARS

- Products are available on the market & incorporated into NCCN and ASCO guidelines

Filgrastim	• Filgrastim-**sndz**	5 of 6 reference product indications
	• Filgrastim-aafi	5 of6
Tbo-Filgrastim	• 351 (a), **not a biosimilar**	1 of 6
Pegfilgrastim	• Pegfilgrastim-jmdb	1of 2
	• Pegfilgrastim-cbqv	1of 2
Epoetin alpha	• Epoetin alfa-epbx	2 of 2

Biosimilar product information. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information.
Hematopoietic Growth Factors. National Comprehensive Cancer Network. Version 2.2019. NCCN.org.
Smith JT, et al. Recommendations for the use of WBC growth factors: American society of clinical oncology practice guideline update. J Clini Oncol. 2015.
Bohlius J, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. J Clinc Oncol. 2019.
Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information.

THERAPEUTIC ONCOLOGY BIOSIMILARS

Bevacizumab	• Bevacizumab-awwb*	5 of 6 indications
	• Bevacizumab-bvzr	5 of 6
Rituximab	• Rituximab-abbs	1of 6 indications
	• Rituximab-pvvr	4 of 6 indications
Trastuzumab	•Trastuzumab-pkrb	1 of 2 indications
	•Trastuzumab-dkst	2 of 2
	•Trastuzumab-dttb	2 of 2
	•Trastuzumab-qyyp	2 of 2
	•Trastuzumab-anns*	2 of 2

- Starred (*) products are available on the market, launched in July 2019
  - Being evaluated for use as formulary at our institution

Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information.
Biosimilar product information. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information.

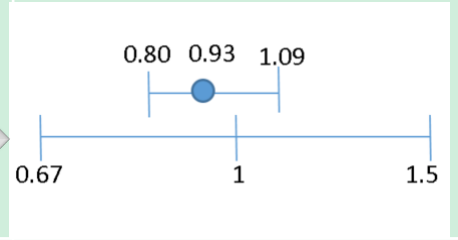
THERAPEUTIC ONCOLOGY BIOSIMILARS: FDA APPLICATION PACKAGES

- Pharmacology
  - Single dose PK studies in healthy males
  - Several biosimilars (6 out of 9) compared US & EU product to itself
    - Then used EU as comparator arm in clinical trial
- Clinical Studies
  - Equivalence or non-inferiority design
    - Reminder that equivalence design does not mean products are equivalent
  - Pre-specified surrogate endpoints as primary objective
  - Immunogenicity and adverse events evaluated

Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information.
Biosimilar product information. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information.

THERAPEUTIC ONCOLOGY BIOSIMILARS: COMPARATIVE CLINICAL STUDIES

Biosimilar	Indication	Study Design	Primary Results	Equivalence Margin
Bevacizumab-awwb	First line NSCLC	Equivalence	Objective response rate ORR risk ratio 0.93 (90% CI, 0.80-1.09) ORR biosimilar 39% vs. US-bevacizumab 41.7%	ORR risk ratio 90% CI of 0.67-1.5
Bevacizumab-bvzr	First line NSCLC	Equivalence	Objective response rate ORR risk ratio 1.015 (90% CI, 0.886-1.163)* ORR biosimilar 45.3% vs. EU bevacizumab 44.6%	ORR risk ratio 90% CI of 0.73-1.137



Thatcher N, et al. Clin Cancer Res. April 1, 2019.

Reinmuth, N, et al. BioDrugs. July 23, 2019.

THERAPEUTIC ONCOLOGY BIOSIMILARS: COMPARATIVE CLINICAL STUDIES

Biosimilar	Indication	Study Design	Primary Results	Equivalence Margin
Rituximab-abbs	First line follicular lymphoma	Non-inferiority	Overall response Difference (one-sided 97.5 CI) 4.3% (-4.25) OR biosimilar 97% vs. US-rituximab 93%	Non-inferiority met if 97.5% CI OR was greater than -7%
Rituximab-pvvr	First line follicular lymphoma	Equivalence	Overall response rate at week 26 ORR difference 4.66 (95% CI -4.16- 13.47) ORR biosimilar 75.5 % vs. EU-rituximab 70.7 %	ORR difference -16 to 16% (95% CI)

Won Seog K, et al. EfficacLancet Haematol. 2017. NCT02213263. Clinicaltrials.gov.

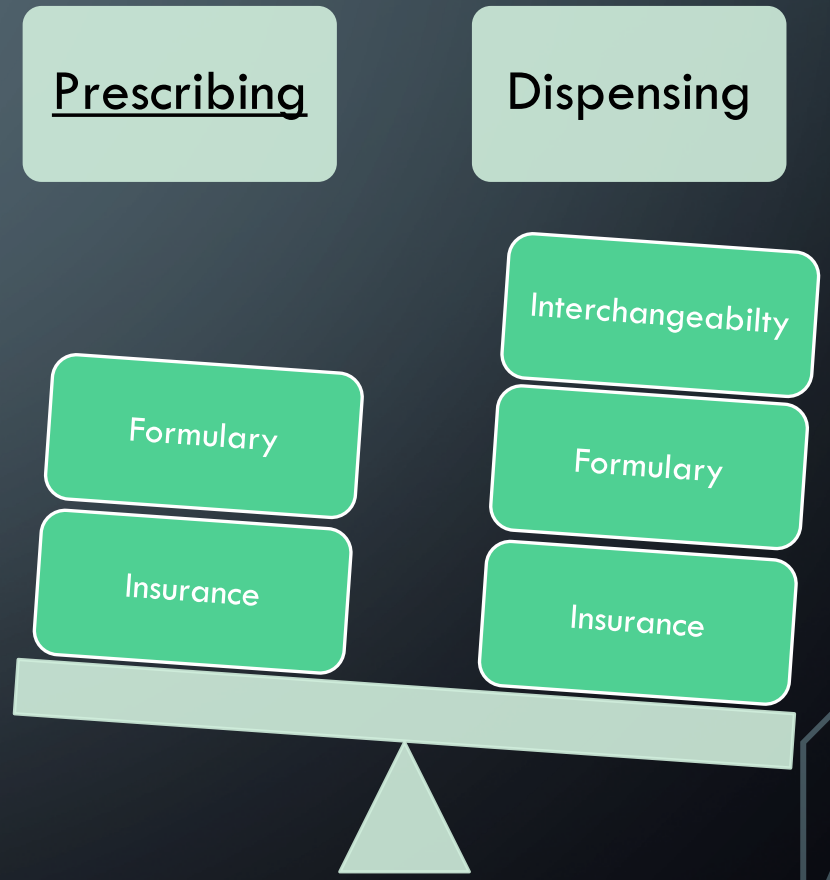
THERAPEUTIC ONCOLOGY BIOSIMILARS: COMPARATIVE CLINICAL STUDIES

Biosimilar	Indication	Study Design	Primary Results	Equivalence Margin
Trastuzumab-pkrb	Neoadjuvant breast cancer	Equivalence	Pathological complete response pCR risk ratio 0.93 (95% CI, 0.78-1.11) pCR biosimilar 46.8% vs. US-trastuzumab 50.4%	pCR risk ratio 95% CI of 0.74-1.35
Trastuzumab-dttb	Neoadjuvant breast cancer	Equivalence	Breast pathological complete response bpCR risk ratio 1.259 (95% CI, 1.085-1.460) bpCR biosimilar 51.7% vs. EU-trastuzumab 42%	bpCR risk ratio 95% CI of 0.785-1.546
Trastuzumab-anns	Neoadjuvant breast cancer	Equivalence	Pathological complete response pCR risk ratio 1.188 (90% CI, 1.033-1.366)* pCR biosimilar 48% vs. EU-Trastuzumab 41%	pCR risk ratio 90% CI of 0.759-1.318
Trastuzumab-dkst	Metastatic breast cancer	Equivalence	24 week overall response rate ORR risk ratio 1.09 (90% CI, 0.974-1.211) ORR biosimilar 69.6% vs. EU-trastuzumab 64%	24 week ORR risk ratio 90% CI of 0.81-1.24
Trastuzumab-qyyp	Metastatic breast cancer	Equivalence	33 week objective response rate ORR risk ratio 0.940 (95% CI, 0.842-1.049) ORR biosimilar 62.5% vs. EU-trastuzumab 66.5%	33 week ORR risk ratio 95% CI of 0.842-1.049

Rugo HS. JAMA. 2017; 317(1). Stebbing J. Lancet Oncol. 2017; 18. Xavier P. J Clin Oncol. Apr 1, 2018; 36(10). Pegram MD. British Journal of Cancer. 2019; 120. VonMinckwitz G. Lancet Oncol. 2018; 19.

BIOSIMILAR PRACTICAL CHALLENGES: PRESCRIBING

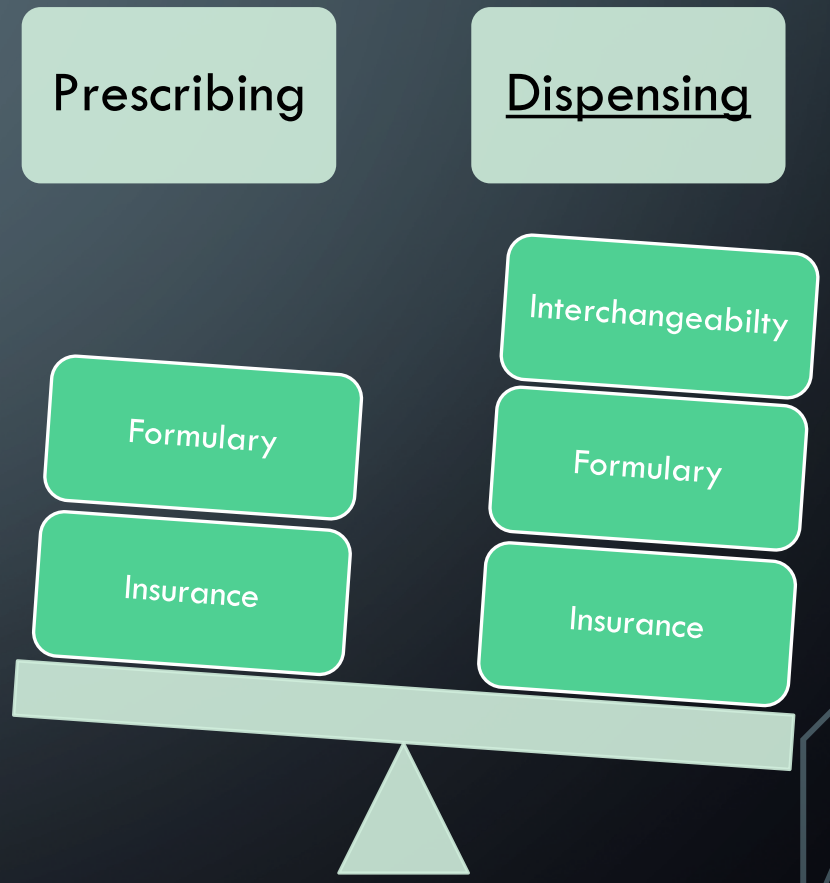
- Caution with names, even in EMR
  - Can be cut short or limited to brand-names only
  - Risk of medication errors: look-alike, sound-alike
  - Inadvertent switching if infusions received at multiple locations
- Provider-specific preference vs. institution formulary decision
- Insurance coverage
- Approved indications only vs. off-label usage
- Comfort level with non-medical switching



Li, E, et al. Pharmacist substitution of biological products: issues and considerations. JMCP. July 2015.

BIOSIMILAR PRACTICAL CHALLENGES: DISPENSING

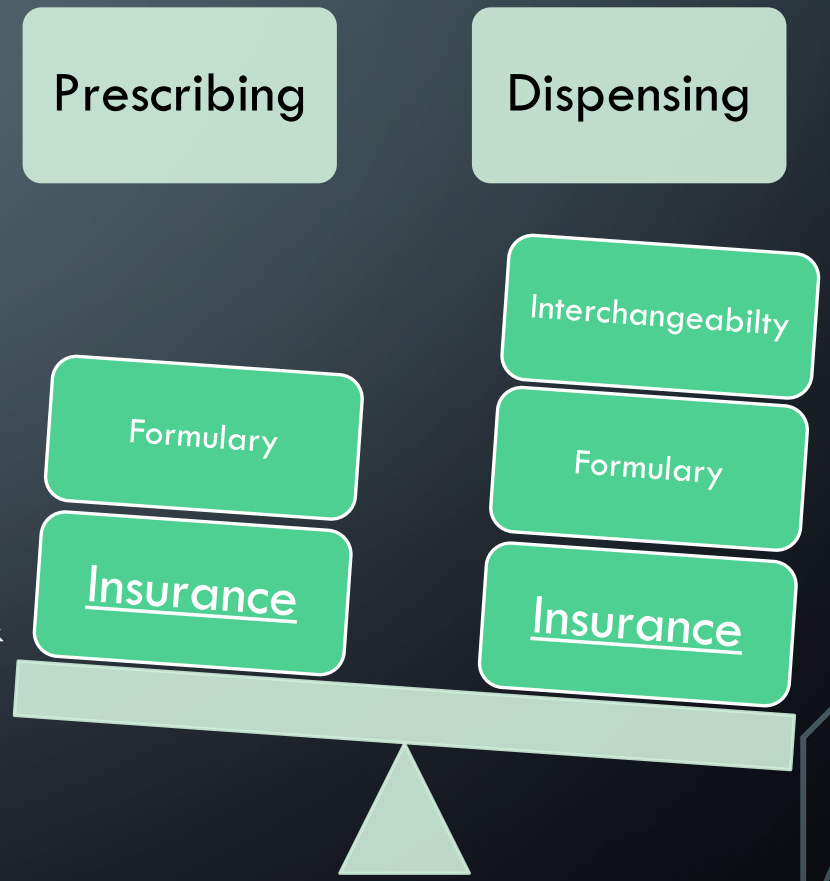
- Substitution of an non-interchangeable product is not allowed <u>except</u>:
  - Therapeutic interchange to maintain a formulary with a policy/procedure from a P&T committee
    - Based on extensive clinical & economic review
    - Voted on by pharmacy and providers
    - Decisions to stock/dispense 1 product
    - Automatic substitution by pharmacy pre-approved & agreed upon by providers
- Interchangeability status granted through FDA
  - State Laws must be followed



Li, E, et al. Pharmacist substitution of biological products: issues and considerations. JMCP. July 2015.

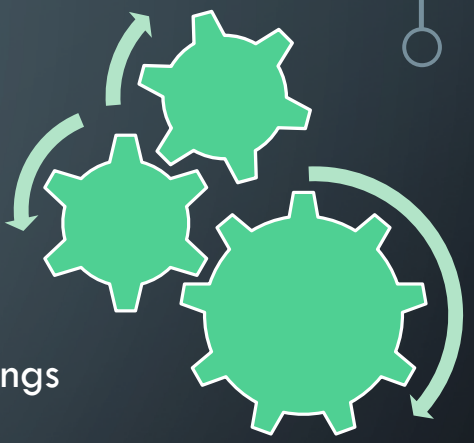
BIOSIMILAR PRACTICAL CHALLENGES: INSURANCE

- Payers are working to influence prescribing
  - Biosimilar preferred agent
  - Reference product requires a PA
  - Not covering the non-preferred products
    - Costly for patients & institutions!
- Insurance review prior to dispensing
  - Time/resource consuming
  - Does this mean pharmacy would stock every biosimilar & reference product
    - Multiple Look-Alike, Sound-alike products increases the risk of medication errors at the point of prescribing & dispensing



Li, E, et al. Pharmacist substitution of biological products: issues and considerations. JMCP. July 2015.

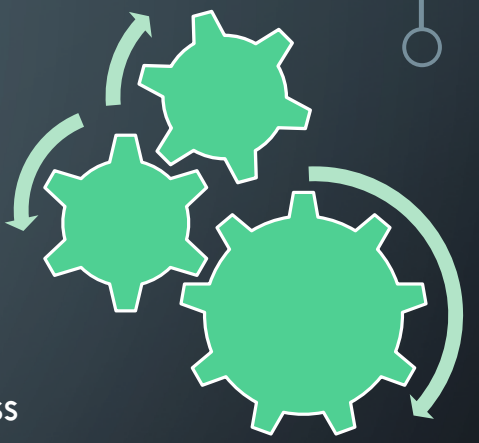
WHEN WILL WE SEE THERAPEUTIC ONCOLOGY BIOSIMILARS IN CLINICAL PRACTICE?



- Market Availability
  - Hindered by complicated contracting (manufacturer, wholesaler, insurance, PMB)
    - Rebates based on utilization of a reference product can overcome biosimilar cost savings
  - Reference product manufacturers will not go quietly!
    - Legal battles
    - Direct to consumer advertising: brand loyalty
- Cost Savings
  - Potentially not what we thought due to increased costs of the complicated manufacturing process
  - Cost of required switching studies to reach interchangeable status may negate all cost saving potential

Simmons-Stern N, et al. The state of US biosimilars market access: payer perceptions of past, present and future hurdles to adoption. Trinity Partners. Jan 2018.

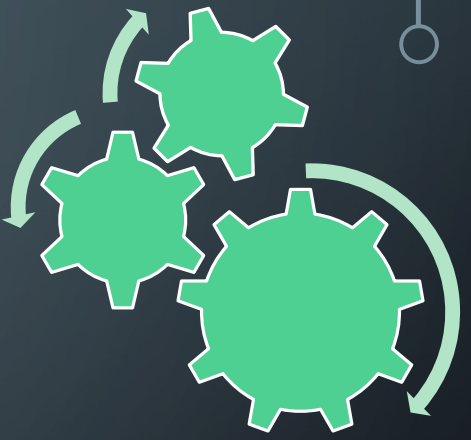
WHEN WILL WE SEE THERAPEUTIC ONCOLOGY BIOSIMILARS IN CLINICAL PRACTICE?



- Oncology community
  - Clinical confidence & mainstream acceptance is low
    - In oncology, if it doesn't work you don't get a second chance
    - FDA has robust educational materials for patients & providers on the approval process
- Survey of 77 oncologists completed in 2018
  - Most important factors impacting the decision to prescribe a biosimilar
    - Safety and efficacy
    - Cost
  - 41.6% increase in the likelihood that an oncologist would prescribe a biosimilar if it was designated as interchangeable
    - Better demonstration of efficacy
  - Concerns about pharmacy substituting biosimilars without checking with oncologists

Simmons-Stern N, et al. The state of US biosimilars market access: payer perceptions of past, present and future hurdles to adoption. Trinity Partners. Jan 2018.
Cook JW, et al. Academic oncology clinician's understanding of biosimilars and information needed before prescribing. Ther Adv Med Oncol. 2019.

WHERE CAN WE FIND THE DATA?



- Biosimilar safety & efficacy data are not included in the label
  - The FDA approved label contains the clinical data from the reference product
    - Extrapolation from the biosimilar approval pathway allows the biosimilar to utilize the safety and efficacy data from the reference product because it has been deemed "highly similar"
- Comparative clinical trials used in the biosimilar applications are published
  - Hard to find because several use their R&D name

FDA website → Approval Packages → FDA Application Review Files → Clinical Pharmacology Biopharmaceutics Review → Summary of relevant clinical studies

Drug Approval Package: OGIVRI (Trastuzumab-dkst)

Company: Mylan GmbH
Application Number: 761074
Approval Date: 12/01/2017

Drugs@FDA information available about OGIVRI

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)
- Medical Review(s) (PDF)
- Chemistry Review(s) (PDF)
- Pharmacology Review(s) (PDF)
- Statistical Review(s) (PDF)
- Clinical Pharmacology Biopharmaceutics Review(s) (PDF)
- Proprietary Name Review(s) (PDF)
- Other Review(s) (PDF)

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761074Orig1s000TOC.cfm

Table 2. Summary of relevant clinical studies

Protocol	Title	Subjects	Objectives	Route/Dose/Duration
PK Similarity Study				
MYL-HER-1002	A single-dose, randomized, double-blind, 3-arm, parallel-group study designed to compare the pharmacokinetic profiles of MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin in healthy subjects.	Healthy (N=120)	PK similarity	Single IV 8 mg/kg
Comparative Clinical Study				
MYL-HER-3001	A multicenter, randomized, double-blinded, parallel group design to assess the efficacy and safety of MYL-1401O compared to EU-approved Herceptin plus docetaxel or paclitaxel in patients with HER2-positive MBC	MBC (N=642)	Efficacy, safety, immuno-genicity	Loading dose 8 mg/kg IV followed by a maintenance dose 6 mg/kg Q3W with docetaxel 75 mg/m^2 or paclitaxel 80 mg/m^2 Q3W

PK: pharmacokinetics; IV, intravenous; MBC: metastatic breast cancer

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761074Orig1s000TOC.cfm

WHERE CAN WE FIND THE DATA?

- Pharmacovigilance
  - Ongoing post approval safety & efficacy monitoring
  - Limited by inconsistent reporting or reporting inaccurate products
- Literature reviews comparing non-medical switching from reference to biosimilar
  - 2018 review of 90 studies demonstrated no difference in safety and efficacy
    - 7 filgrastim biosimilar studies
      - 2 included oncology populations

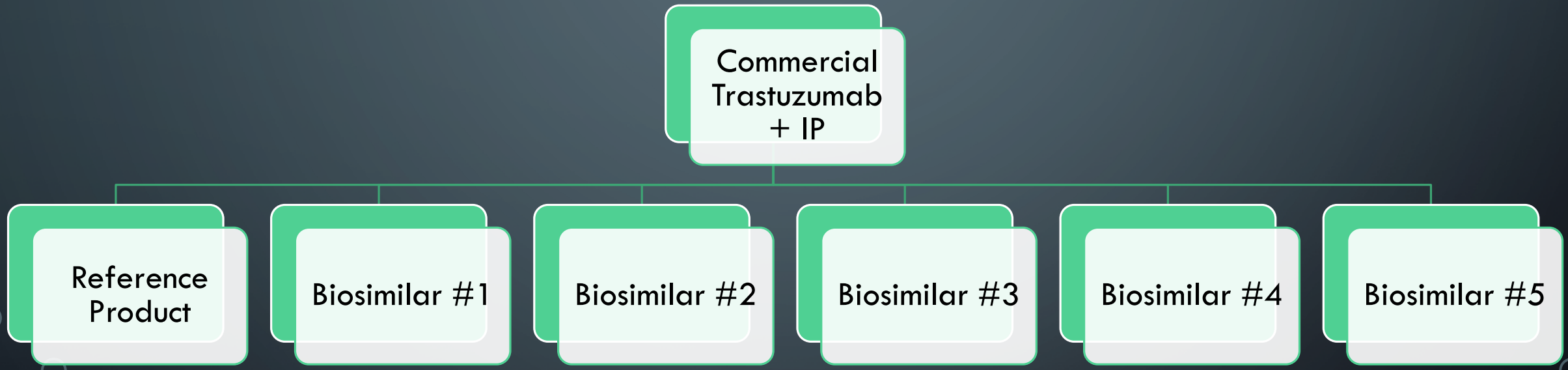
Cohen HP, et al. Switching reference medicines to biosimilars: a systematic literature review of clinical outcomes. Drugs. 2018.
Giezen TJ, et al. Pharmacovigilance of biosimilars: challenges and possible solutions. GaBI Journal. 2012.
Grampp G, et al. Pharmacovigilance considerations for biosimilars in the USA. BioDrugs. 2015.

BIOSIMILAR IMPACT: CLINICAL PRACTICE

Provider prescribes Trastuzumab → Pharmacy dispenses Trastuzumab-anns

- Prescribing
  - EMR limitations
  - Look-alike, sound-alike
  - Non-Medical Switching
- Dispensing
  - Interchangeable status → State laws
  - Therapeutic interchange in place → Formulary substitution
  - Look-alike, sound-alike
  - Inventory management
- Insurance Impact?

BIOSIMILAR IMPACT: CLINICAL RESEARCH



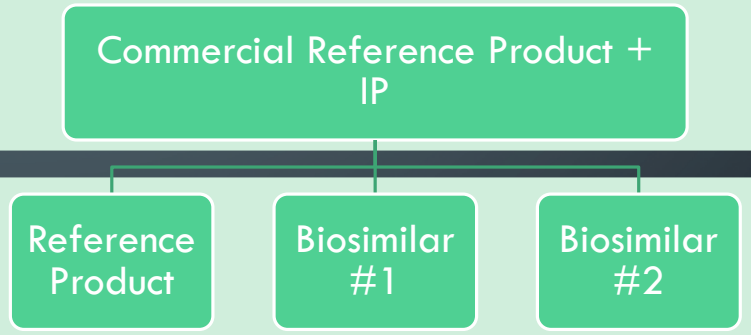
- Research with multiple biosimilars on the market

BIOSIMILAR IMPACT: CLINICAL RESEARCH

- Exclude biosimilars?
  - Negatively impact study participation
  - Impractical due to institutional formularies

Protocol language will need to include "or biosimilars"

What impact will this have on the primary objective of the trial?



- Document which specific product is used
  - Consider stratifying results by product to identify safety or efficacy signals
- Will anyone conduct large scale comparative studies using commercial products to compare biosimilar & reference product efficacy?

SUMMARY

- Generics are not biosimilars & therefore each has a specific FDA approval pathway & requirements
- Biosimilar approval takes into account the totality of the evidence
  - Analytical, nonclinical, pharmacology, clinical studies
- Practical challenges will require clear communication
  - Prescribing, dispensing, research