Addressing Barriers to Biosimilar Integration in Cancer Care

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Provided by ASHP

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- Sandra Cuellar- speakers bureau for Genentech; advisory board for Coherus Biosciences, Inc.

Learning Objectives

- Summarize the FDA regulatory framework to evaluate biosimilars.
- Describe the application of clinical trial data and requirements for extrapolation of indications and interchangeability of biosimilars.
- Illustrate the biosimilar launch and practice implementation challenge along with best practices to overcome these barriers.
- Describe biosimilars' role under value-based care and potential economic impact.

How many oncology patients on biologics do you personally provide care to each week?

a. Less than 25
b. 26-75
c. 76-125
d. More than 125
e. None - I am not directly involved in patient care

Rational Medicine Use

Patients receive medications appropriate to their clinical needs

- Doses that meet their individual requirement
- For adequate period of time
- At the lowest cost to them and their community

World Health Organization

https://apps.who.int/medicinedocs/pdf/h3011e/h3011e.pdf. Accessed October 30, 2019.

Trends in Healthcare Expenditures

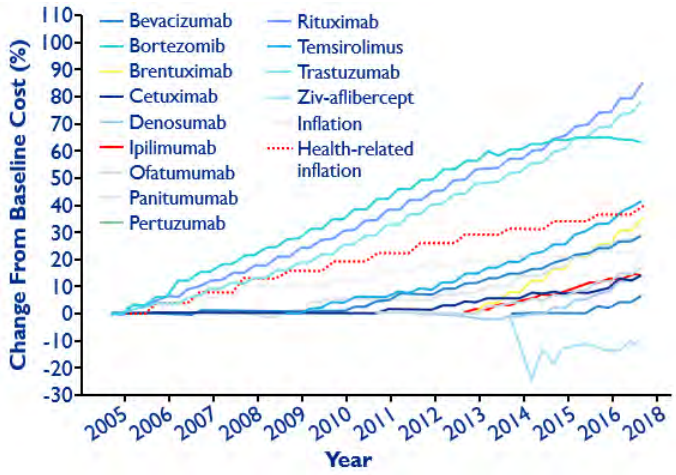
- Global spending on medicines reached $1.2 trillion in 2018 and is set to exceed $1.5 trillion by 2023
- United States pharmaceutical expenditures increased 5.5% in 2018 for a total of $476.2 billion
- Patient out-of-pocket costs increased to $61 billion

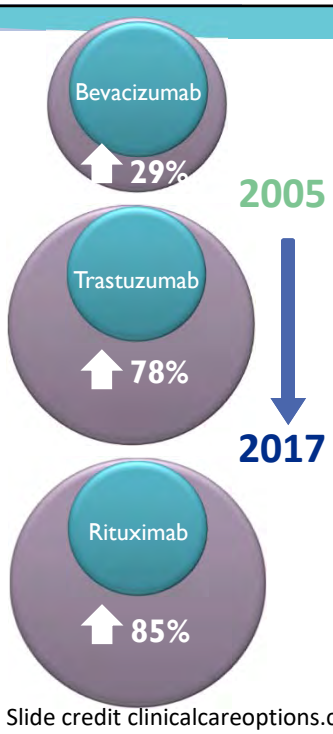
Top Antineoplastic Drugs by Expenditures in U.S. Clinics in 2018

Drug	Expenditures ($ Thousands)	% Increase from 2017
Nivolumab	3,433,985	35.4
Pembrolizumab	3,372,394	88.4
Rituximab	2,882,704	2.6
Trastuzumab	2,471,007	8.8
Bevacizumab	2,378,412	1.1
Pertuzumab	1,126,661	32.2
Daratumumab	998, 628	43

https://apps.who.int/medicinedocs/pdf/h3011e/h3011e.pdf. Accessed October 30, 2019.

Biologic Inflation Over Time





Gordon N et al. *J Clin Oncol*. 2017; 36:319-25. Slide credit clinicalcareoptions.com

Biosimilars are Needed to Disrupt Pharmaceutical Biologic Ecosystem

- Biologics have revolutionized the treatment of cancer
- Biologics are expensive and costs have increased progressively
- Introduction of biosimilars increase competition with biologic reference (originator biologic) without compromising quality
- Biologic Price and Competition & Innovation Act of 2009 (BPCI)

Li EC et al. *J Mana Care Spec Pharm*. 2015; 21:532-9. Dörner T et al. *Nat Rev Rheumatol*. 2015; 11:713-24.
FTC Report—Emerging Health Care Issues: Follow-on Biologic Drug Competition. June 2009.
FDA. *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry*. April 2015.

Biosimilar versus Innovator Biologic

- Abbreviated licensure pathway
- Biologic production & manufacturing cost >> small molecule
- Require different scientific data compared to innovator for FDA approval

Biosimilar
- Development time: >8 – 10 years
- Development Costs: $100 - 200 million

Innovator Biologic
- Development time: ~15 years
- Development Costs: $800 million – 1 Billion

www.optum.com/resources/library/potential-pitfalls-biosimilars.html. Accessed Nov 1, 2019.
FDA. *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry*. April 2015.

Selected FDA Approved Oncology Biosimilars

- **Bevacizumab (Avastin)**
  - Bevacizumab-awwb (Mvasi)
  - Bevacizumab-bvzr (Zirabev)
- **Trastuzumab (Herceptin)**
  - Trastuzumab-anns (Kanjinti)
  - Trastuzumab-dttb (Ontruzant)
  - Trastuzumab-qyyp (Trazimera)
  - Trastuzumab-pkrb (Herzuma)
- **Rituximab (Rituxan)**
  - Rituximab-Abbs (Truxima)
  - Rituximab-Pvvr (Ruxience)

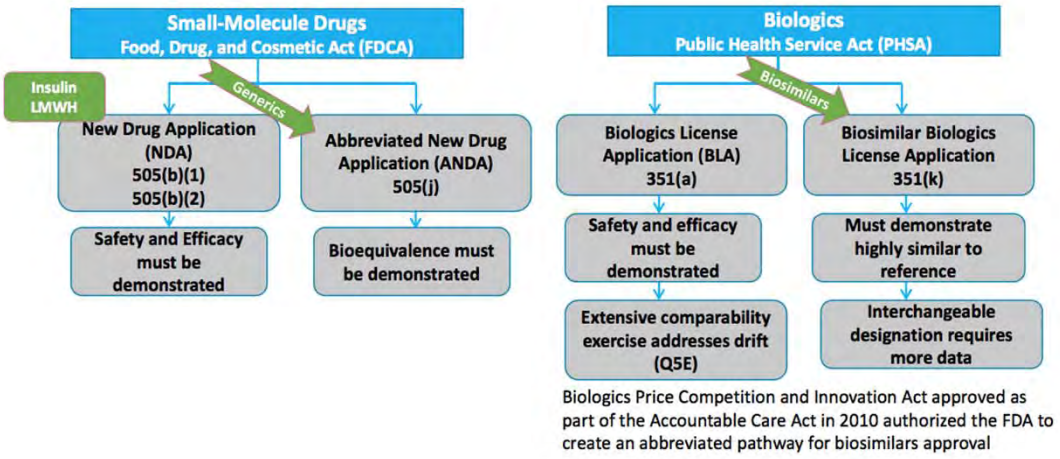
Regulatory Framework for Biosimilars

FDA Definition of Biosimilar

- "The biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components, and there are **no clinically meaningful differences** between the biosimilar product and the reference product in terms of **safety, purity, and potency of the product.**"
- Must utilize same mechanism of action for the condition prescribed
- Must utilize same route of administration, dosage form, strength, and proposed condition to reference product
- Expected to produce same clinical result in any given patient

www.fda.gov/media/114574/download. Updated July 2018. Accessed November 17, 2019.

FDA Approval Pathway



FDA. Federal Food, Drug, and Cosmetic Act (FD&C Act). Updated 2017.

How Do Clinical Development Pathways for New Biologics vs. Biosimilars Compare?

Study Phase	New Biologic – 351(a)	Biosimilar – 351(k)
Preclinical and animal toxicology studies	▪ Defines pharmacologic, toxicologic effects prior to human studies	▪ Structural/functional analyses ▪ Animal studies including assessment of toxicity
Phase I and II	▪ Dose and schedule determined; immunogenicity assessed ▪ Clinical activity and safety evaluated in given pt population	▪ Human PK, PD, immunogenicity compared to reference biologic
Phase III	▪ Assessed in large population to confirm therapeutic benefit	▪ If requested by FDA because of residual uncertainty, typically designed to demonstrate equivalence or noninferiority to reference biologic

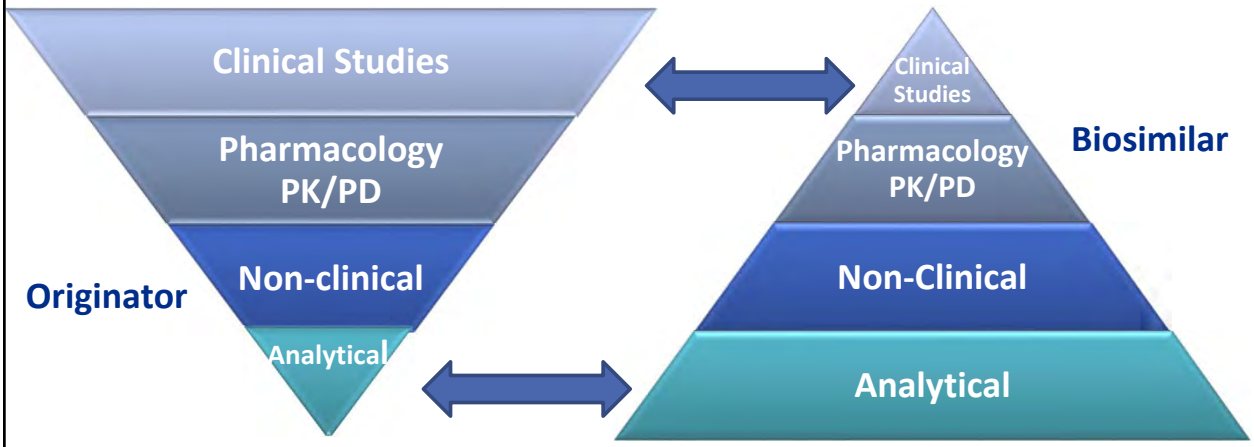
All studies required by FDA

At each step, FDA determines if further studies are needed

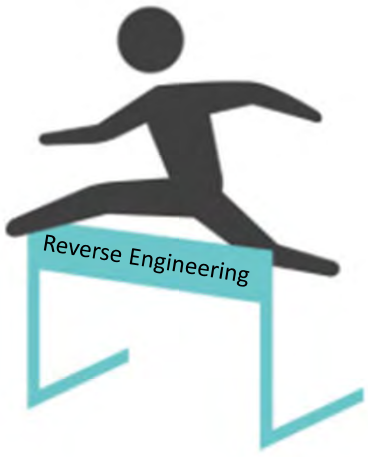
Kingham R et al. In: Wang W et al. Biological Drug Products: Development and Strategies, First edition. 2014. Alten R et al. *Semin Arthritis Rheum*. 2015; 44(6 suppl):S2-8. FDA. *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry*. April 2015.

Biosimilar Pathway Represents a Paradigm Shift from Standard Originator Registration Pathway

Establish biosimilarity based on totality of evidence, not reestablish benefit



www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval. Updated October 20, 2017. Accessed September October 20, 2019.



Biosimilars Must Demonstrate Comprehensive Comparability to Reference Biologic Testing

Identification of Critical Quality Attributes of Reference Product
• Characteristics that are essential for biologic function and ultimately for safety and efficacy
• Clearly defined attributes
• Measurable attribute
• Must be monitored on an ongoing basis

Lucio SD et al. *Am J Health Syst Pharm*. 2013; 70:2004-17. Li EC et al. *J Mana Care Spec Pharm*. 2015; 21:532-9.

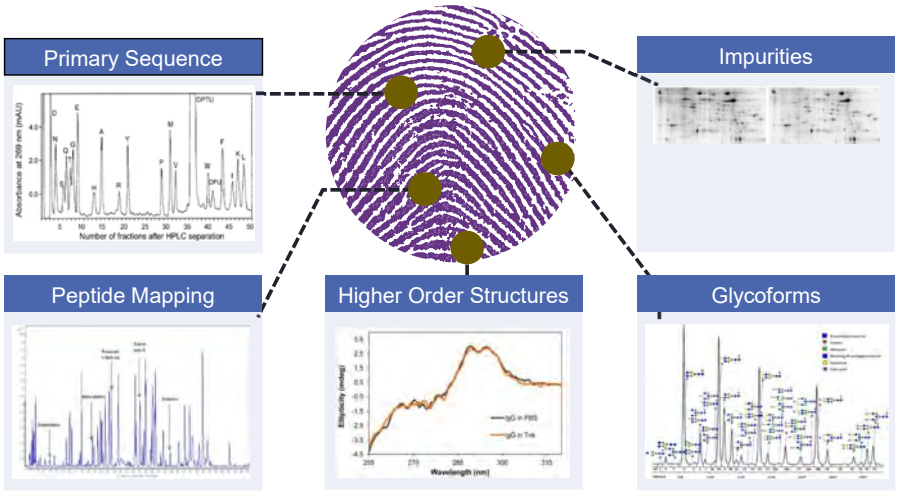
Typical Structure and In Vitro Assessment for Monoclonal Antibody Biosimilar

- Monoclonal antibody may have >40 attributes identified
- Attributes may be evaluated using >50 different assays
- Scientific understanding of how this attributes influence safety, efficacy, immunogenicity and/or PK/PD is critical for biosimilar success

Category	Attribute
Fab-mediated biologic activity	Potency Receptor binding Receptor signaling Receptor specificity
Fc-mediated biologic activity	Binding to FcRN Complement-dependent cytotoxicity
Primary structure	Molecular weight Protein sequence Glycosylation
High order structure	Secondary & tertiary structure

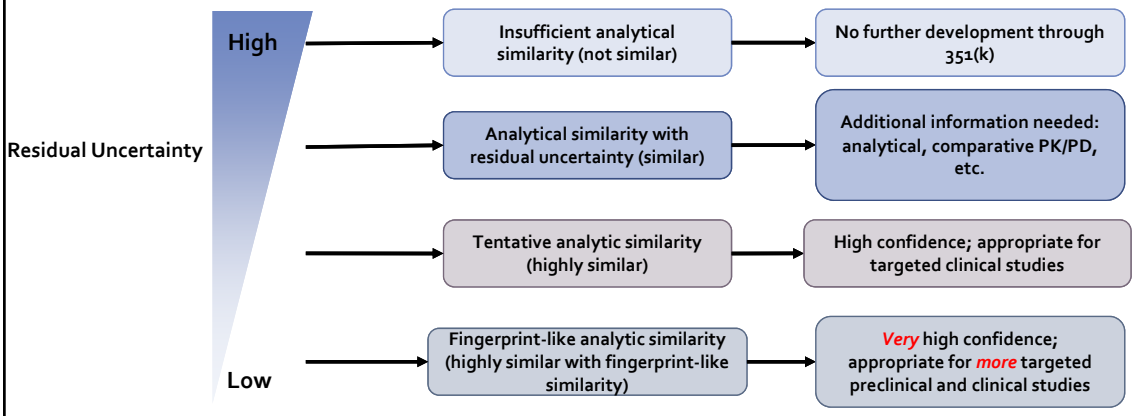
Thill M et al. *Future Oncol*. 2019; 15:1147-65.

Establishing Fingerprint-Like Similarity: Physiochemical Properties

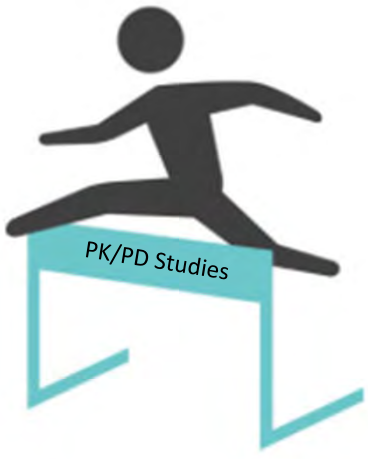


FDA. *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product: Guidance for Industry.* December 2016.

Preclinical Assessment: 4 Levels of Analytical Characterization



FDA. *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product: Guidance for Industry.* December 2016.



Biosimilars Must Demonstrate Comprehensive Comparability to Reference Biologic Testing

Equivalent Pharmacokinetics (PK)

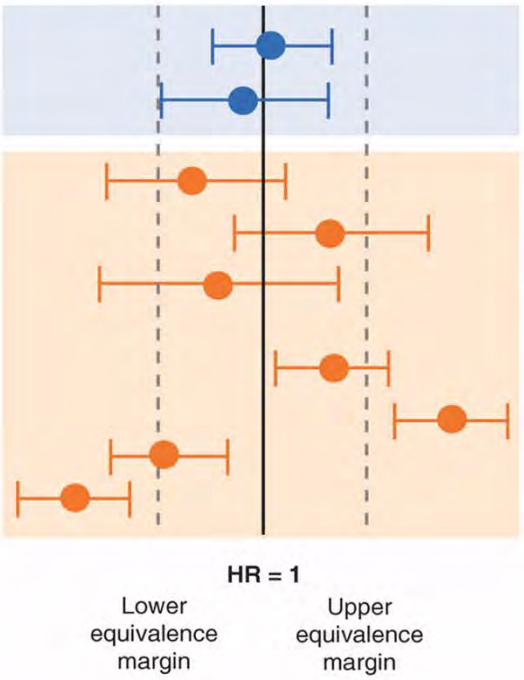
- Comparative PK human studies required
- Comparative PD human studies where clinical relevant markers available
- 'go/no go' step for biosimilars

FDA. *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry*. April 2015.
Isakov L et al. *Am J Ther*. 2016; 23:e1903-10.

Biosimilars Clinical Trial Characteristics

- Performed in populations that are sensitive to detect clinically meaningful differences between the biosimilar and reference product
- Demonstrate that the biosimilar candidate is neither decreased or increased efficacy, and does not have an increased safety risk compared to reference product
- Endpoints need to be sensitive enough to detect a difference in activity if one exists

Markus R et al. *Biodrugs.* 2017; 31:175-87.



Equivalence met

Equivalence not met

- Equivalence not met
- Biosimilarity not demonstrated

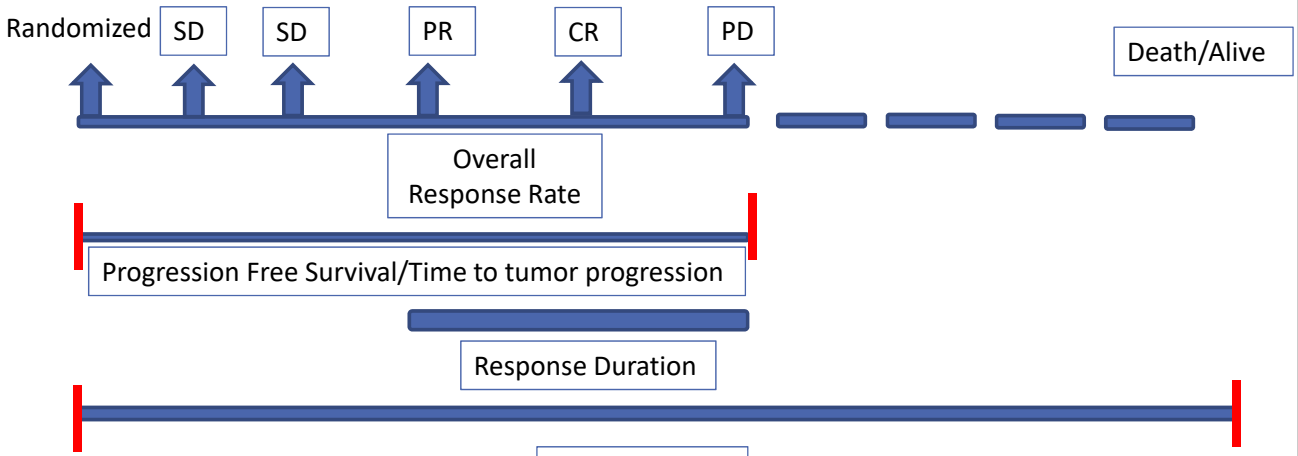
The biosimilar is neither better nor worse than the reference product:

- Clinical similarity based on predetermined equivalence margins
- 95% CIs recommended for assessing clinical equivalence

Thill M et al. *Future Oncol*. 2019; 15:1147-65.

Clinical Review of Oncology Biosimilars

Oncology Endpoint Definitions



Stable disease = SD
Partial Response = PR
Complete Response = CR
Progressive Disease = PD

FDA. *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics: Guidance for Industry.* December 2018.

Endpoints to Establish Biosimilarity

Traditional Clinical Endpoints

- Demonstrate a specific clinical benefit
  - Overall survival
  - PFS
    - Metastatic setting
  - Disease-free survival
    - Curative setting
- Time & cost considerations

Biosimilar Endpoints

- Measure activity and correlate with long-term endpoints
  - Overall Response Rate (ORR)
  - Pathologic complete response (pCR) rate
- OS and PFS may not be sensitive to demonstrate comparability
  - Tumor burden, performance status, previous or later lines of therapy

Zhang N et al. *GaBi J*. 2014; 3:21-5.
Rugo HS et al. *Cancer Treatment Reviews*. 2016; 46:73-9. Thill M et al. *Future Oncol*. 2019; 15:1147-65.

Case Study: Bevacizumab Biosimilar

Sensitive Population Options

- Non-small cell lung cancer (NSCLC)
- Metastatic colon cancer
  - Less sensitive, adding bevacizumab increased PFS without significant increase in overall response rate (ORR)

Endpoints Options

- Primary Endpoints
  - ORR
- Secondary Endpoints
  - Risk difference of ORR
  - PFS
  - Duration of response (DOR)
  - Safety
  - Overall Survival (OS)

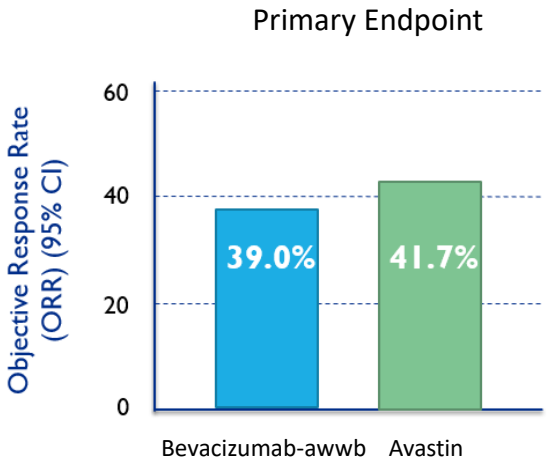
Trial Design Options

- Equivalence study
- Non-inferiority study

Hurwitz H et al. *N Engl J Med*. 2004; 350:2335-42. Saltz LB et al. *J Clin Oncol*. 2008; 26:2013-19.
Ebbers HC et al. *Drug Discovery Today*. 2013; 18:872-9.

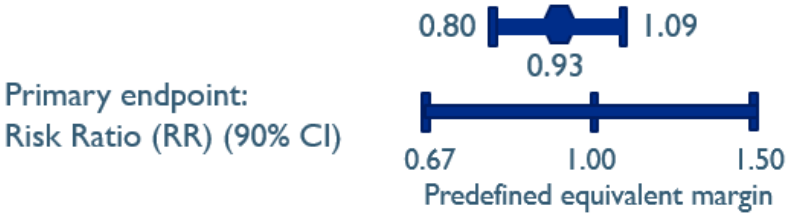
Case Study: Bevacizumab - awwb

MAPLE Trial	N = 642
Design	Phase 3 Equivalence Study
Sensitive Population	NSCLC (non-squamous) receiving receiving 1st line chemotherapy
Endpoints	Primary: ORR Secondary: PFS, DOR, safety, & OS



Cuellar et al. *Am J Health Syst Pharm*. 2019; 76:1725-38.

Equivalence Margins: Bevacizumab – awwb



Cuellar et al. *Am J Health Syst Pharm*. 2019; 76:1725-38.

Bevacizumab-awwb: Secondary Endpoints

Phase III trial in nonsquamous NSCLC	
PFS	• PFS was comparable in the Bev-awwb 60.1% vs. bevacizumab 60.2% • Estimated HR for Bev-awwb relative to bevacizumab was 1.03 (90% CI, 0.83, 1.29)
OS	• Fatal AEs occurred in 4.0% with Bev-awwb vs. Bev 3.6% • OS comparable Bev-awwb 86.7% vs. Bev 88.3%
Incidence of ADAs	• Immunogenicity was similar, Bev-awwb 1.4% vs. Bev 2.5% • No patient developed neutralizing antibodies

ADA = Antidrug Antibody

Cuellar et al. *Am J Health Syst Pharm*. 2019; 76:1725-38.

Case Study: Trastuzumab Biosimilar

Sensitive Population Options	Endpoints Options	Trial Design Options
• Metastatic breast cancer • Early stage breast cancer	• Overall response rates (ORR) • Pathologic complete response (pCR)	• Equivalence • Non-inferiority

Barbier et al. *British J Cancer*. 2019; 121: 199-210.

Case Study: Trastuzumab Biosimilars

- Trastuzumab approval indications
  - Breast cancer (metastatic and early stage)
  - Gastric cancer (metastatic)
- Goal is to select most sensitive and homogeneous population
  - Metastatic breast cancer vs. early breast cancer
    - Metastatic may represent less homogeneous population and thus less sensitive
      - Location of metastases, comorbidities, disease severity, number and type of prior therapies
    - Early breast cancer may have fewer confounding characteristics

Barbier et al. *British J Cancer*. 2019; 121: 199-210.

Case Study: Trastuzumab Biosimilars

- End points
  - ORR
    - Overall Response rate (ORR) is suitable for detecting meaningful differences in activity between the candidate and reference product
  - pCR rate
    - Absence of residual invasive and in situ cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy
    - FDA recognizes pCR as a surrogate marker for accelerated approval
      - Shown to correlate with long-term survival in patients with early breast cancer

FDA. *Guidance for Industry Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval*. 2014.

Summary Trastuzumab Biosimilars: Sensitive Patient Selection and Endpoints

Biosimilar	Brand Name	# of patients	Patient Setting	Primary Endpoint
Trastuzumab-anns	Kanjinti	725	Neoadjuvant & adjuvant breast cancer	Breast and lymph nodes pCR
Trastuzumab-dkst	Ogivir	500	Metastatic Breast Cancer	ORR
Trastuzumab-dttb	Ontruzant	800	Neoadjuvant & adjuvant breast cancer	Breast pCR
Trastuzumab-pkrb	Herzuma	475	Metastatic Breast Cancer	ORR
Trastuzumab-qyyp	Trazimera	707	Metastatic Breast Cancer	ORR

Barbier et al. *British J Cancer*. 2019; 121: 199-210.

Key Takeaways

Biosimilar Clinical Studies
• Aim is not to establish benefit, but confirm biosimilarity

• Clinical development packages may differ among biosimilars
  • Type of trial
  • Clinical endpoint
  • Patient population

• Endpoints for biosimilars need to highlight activity of drug similar to reference product

Barbier et al. *British J Cancer*. 2019; 121: 199-210.

Extrapolation and Interchangeability Paradigm

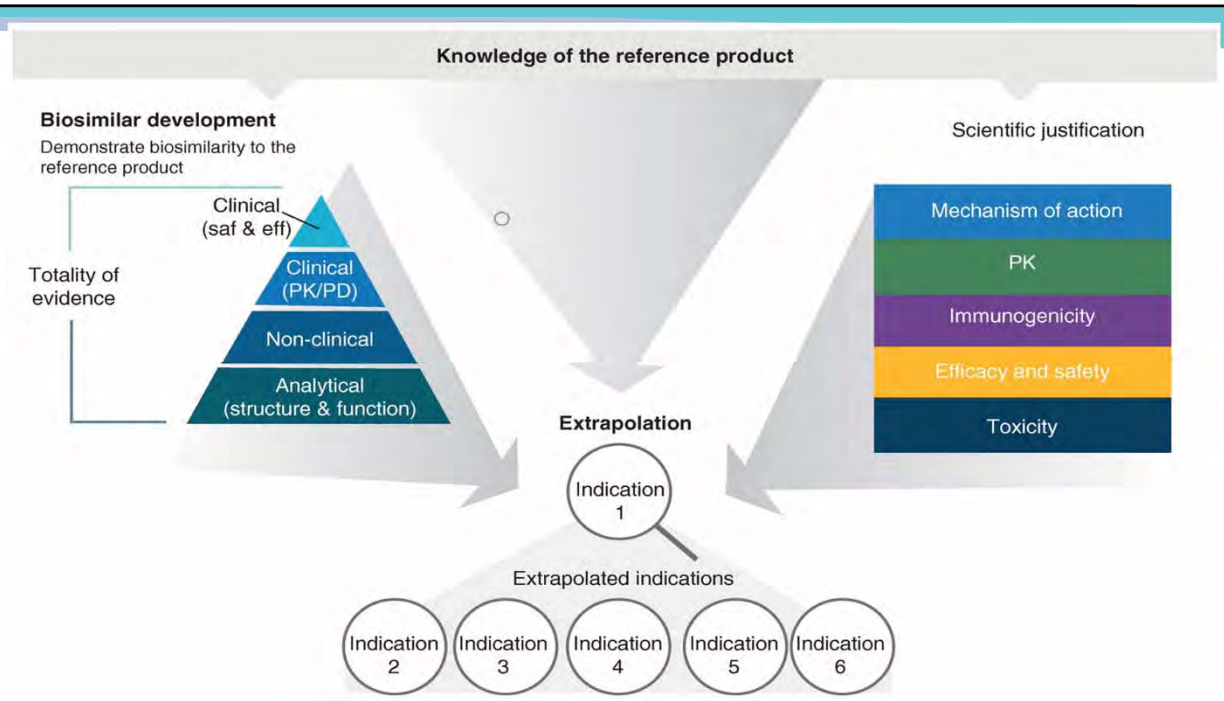
Biosimilar Development & Extrapolation

Demonstrating analytical & functional similarity between biosimilar candidate and its reference product can reduce the number and scope of subsequent clinical trials

If a biosimilar meets the requirements for biosimilarity, **extrapolation of data** may allow for approval of **additional indications** for which the reference product is indicated without other dedicated clinical studies

Key principles for extrapolation include mechanism of action, totality of evidences showing comparability, safety profile without risk of immunogenicity

Lyman GH et al. *N Engl J Med*. 2018; 378:2036-44.



Thill M et al. *Future Oncol*. 2019; 15:1147-65.

Extrapolation Impact

- Economic benefit leading to lower development costs of biosimilar
- When reviewing a formulary consideration, paradigm of evaluating 3 RCTs does not apply to biosimilars
- Review nonclinical considerations, such as cost, product presentation, storage, stability, and product supply reliability

Interchangeability

- Interchangeable is an FDA designation
- Requires different data standards than "biosimilarity" alone
- Dedicated switching study and post marketing monitoring
- An interchangeable product may be substituted for the reference product without intervention of the healthcare provider who prescribed the reference product

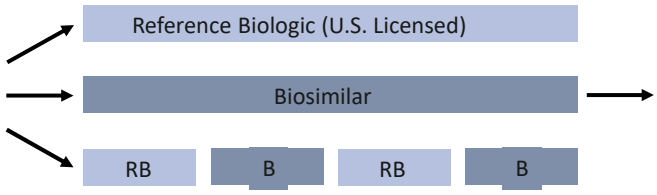
FDA. *Considerations in Demonstrating Interchangeability With a Reference Product: Guidance for Industry*. May 2019.

Biosimilars and Interchangeability

FDA requires additional criteria for interchangeability designation, including demonstration of no loss of safety or efficacy when biosimilar *switched* or *alternated* with, not just compared with, U.S. licensed reference biologic

Study population should be patients, not healthy subjects, but does not need to be the same population used in study showing biosimilarity

Example switch study design:



Study design is flexible, but should include:

- ≥3 switches assures at least 2 exposure periods for each product
- U.S. licensed reference biologic mimics clinical practice in U.S.

FDA. *Considerations in Demonstrating Interchangeability With a Reference Product: Guidance for Industry*. May 2019.

Interchangeability Considerations: State level Regulatory Requirements

- Pharmacists substitution
  - State laws gives pharmacists the authority to act independently of the prescriber to dispense the lowest cost, equivalent medicinal product
  - Prescribers may designate “brand medically necessary”
- State laws vary
  - Prescriber notification and patient notification and consent
- Providing legal immunity for pharmacists who make an interchangeable substitution in accordance with applicable laws
- Keep pharmacy records for a period of 2-3 years

Cauchi R. State laws and legislation related to biologic medications and substitutions of biosimilars. www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx. Accessed November 18, 2019.

Summary

- Biosimilars represent an opportunity to increase access and improve drug expenditures without compromising efficacy, safety, or quality
- Abbreviated pathway approval emphasis is the totality of evidence compared to reference product, not designed to replicate reference product approval pathway
- Pharmacists need to understand extrapolation and interchangeability concepts to better integrate biosimilars into their health systems

Addressing Barriers to Biosimilar Integration in Cancer Care

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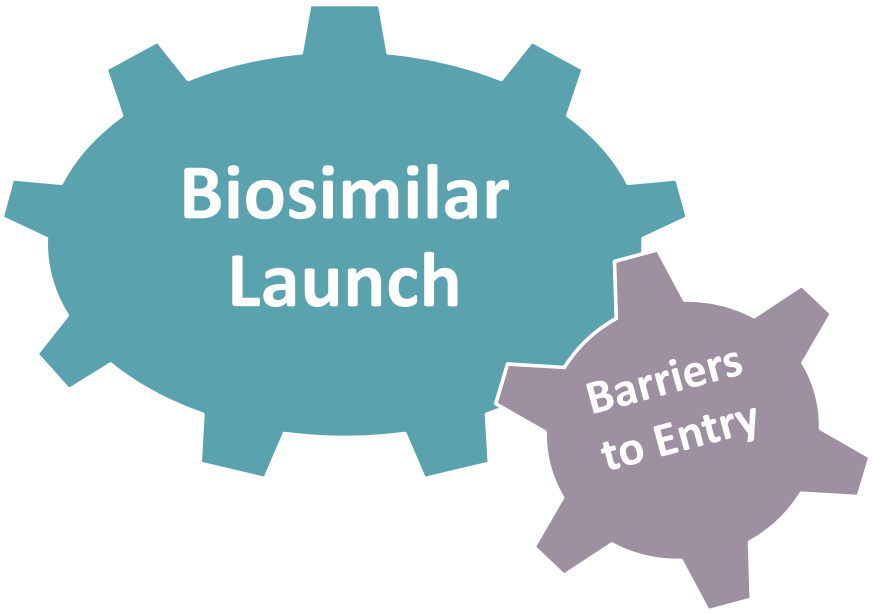
Baptist Health South Florida
Miami, Florida

Learning Objectives

- Illustrate biosimilar launch and practice implementation challenges along with best practices to overcome these barriers
- Describe biosimilars' role under value-based care and potential overall economic impact



Patent Litigation – "Patent Dance"

- Biologics exclusivity under the Biologics Price Competition and Innovation Act
- Several product patents
  - Primary patent on molecule and manufacturing
  - Formulations
  - Delivery systems
  - Absorption
  - Others

Schwieterman P. A Strategic Review of Biosimilars in Oncology Practice. *Hematology/Oncology Pharmacy Association (HOPA) News*. 2018; 15(1). Wechsler J. FDA Struggles to Advance Biosimilars. PharmExec.com Commercial Insights for the C-Suite. 2018; 38(9).

Patent Litigation

- Infringement litigation
- Affecting most biosimilars; months to years of delays
- **CASE – Adalimumab**

Schwieterman P. A Strategic Review of Biosimilars in Oncology Practice. *Hematology/Oncology Pharmacy Association (HOPA) News*. 2018; 15(1). Wechsler J. FDA Struggles to Advance Biosimilars. PharmExec.com Commercial Insights for the C-Suite. 2018; 38(9).

Patent Litigation

- Reference manufacturer may settle biosimilar patent litigation
  - Avoiding legal costs
  - Allowing biosimilar faster market penetration
  - Exchange for royalties
  - Likely to inflate biosimilar price
- Legislation

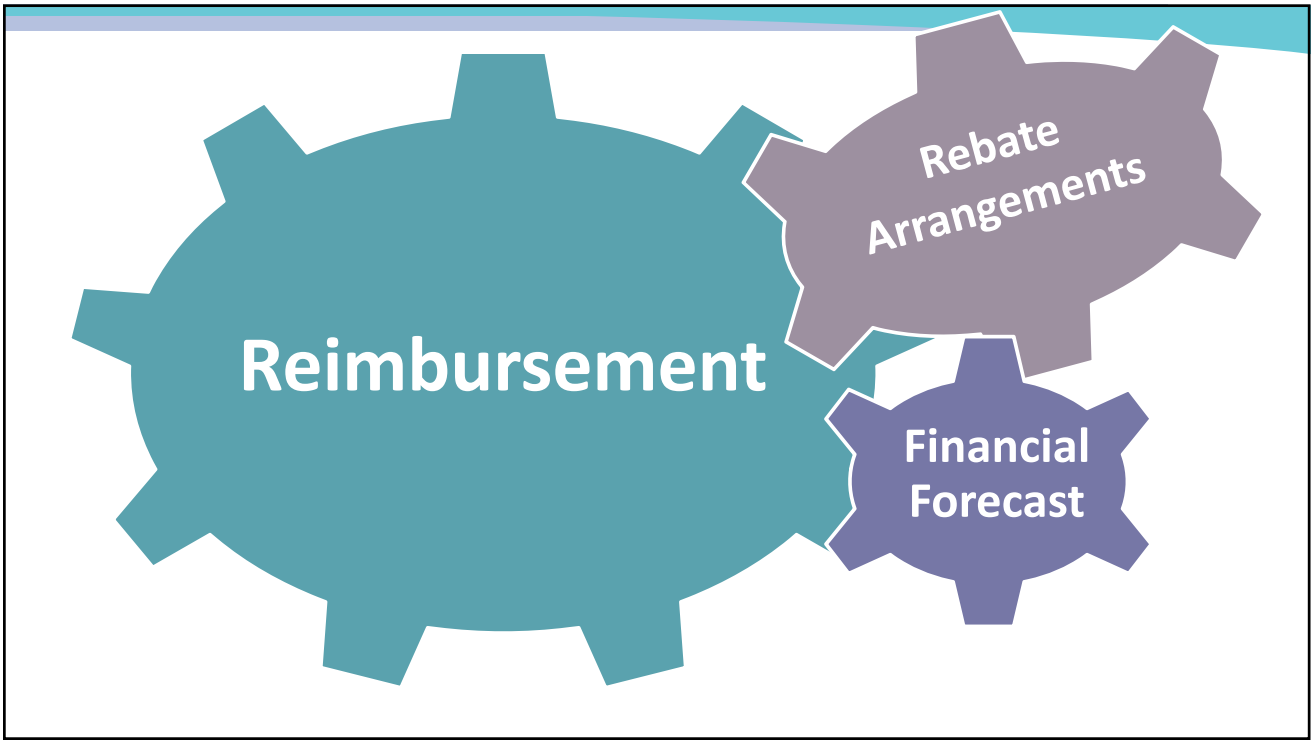
Lyman G et al. Rationale, Opportunities, and Reality of Biosimilar Medications. *N Engl J Med*. 2018; 378:2036-44. Mehr SR et al. Factors Influencing the Economics of Biosimilars in the US. *J Medical Economics*. 2017; 20:1268-71.

Advisory Board Company Poll

What is the biggest barrier to using biosimilars at your cancer program?

Reimbursement	33%
Provider reluctance	31%
Operational Challenges	28%
Other	6%
Patient reluctance	1%

"Managing Oncology Drug Cost" Live Poll. Advisory Board Company. 6/13/2019.



Biosimilar Reimbursement

- Medicare, Medicaid, and commercial payers have all approached biosimilar reimbursement differently
- Eroding revenue landscape
  1. New reimbursement models
  2. Margin declines
  3. Cuts from payer and government agencies

Wechsler J. FDA Struggles to Advance Biosimilars. PharmExec.com Commercial Insights for the C-Suite. 2018; 38(9). Nabhan C et al. Barriers to Oncology Biosimilars Uptake in the United States. *The Oncologist*. 2018; 23:1261-65. Lyman G et al. American Society of Clinical Oncology Statement: Biosimilars in Oncology. *J Clin Oncol*. 2018; 36:1260-5.

Biosimilar Reimbursement

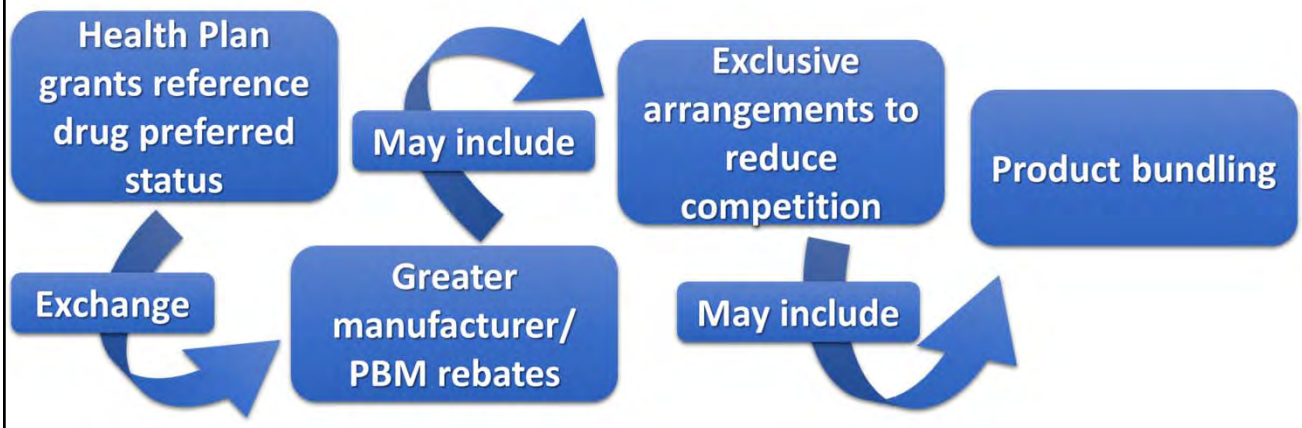
[2018]

- CMS codes each biosimilar separately with independent ASP
- CMS payment based on ASP + "administrative fee" (% reference ASP)
- CMS pass through for eligible entities

CMS = Centers for Medicare and Medicaid Services, ASP = Average Selling Price

DiGrande S. UnitedHealthcare Names 3 Biosimilars Preferred Treatment in 2019 MA Plans. Centers for Biosimilars. October 17, 2018.

Rebate Arrangements – "Rebate Trap"



PBM = Pharmacy Benefits Manager

Nabhan C et al. Barriers to Oncology Biosimilars Uptake in the United States. *The Oncologist*. 2018; 23:1261-65.
Mehr S et al. Factors Influencing the Economics of Biosimilars in the US. *J Medical Economics*. 2017; 20:1268-71.

Rebate Arrangements

- Rebate arrangement on the eve of biosimilar launch
- Multi-million dollar reductions for large health plans
- Payer resources needed to organize switch
- Payer-practice formulary misalignment
  - Impact on economies of scale for volume discounts

Wechsler J. FDA Struggles to Advance Biosimilars. PharmExec.com Commercial Insights for the C-Suite. 2018; 38(9).
Lawless G. Overcoming Challenges in the Emerging Biosimilar Landscape. *J Managed Care Medicine*. 2017; 20(4).

Rebate Arrangements

- Rebates generally not designed to be shared with patients in the form of lower out-of-pocket cost
- **CASE – UnitedHealthcare**
- Reimbursement reform that tackles these rebate incentives is in its infancy
- Highly controversial / advocacy work

Mehr S et al. Factors Influencing the Economics of Biosimilars in the US. *J Medical Economics*. 2017; 20:1268-71. Conti R. *Biosimilars: Reimbursement Issues in Your Oncology Practice.* American Society of Clinical Oncology. Vol. 13. Sept 2017.

Biosimilar Reimbursement

- Biosimilars yield lower net revenue, relative to reference product, assuming (1) commercial payer (2) consistent charge methodology

ASP (acquisition cost) x **mark-up (4-6+ factor)** = **$Charge**

Reimbursement = %**$Charge**

Schwieterman P. A Strategic Review of Biosimilars in Oncology Practice. *Hematology/Oncology Pharmacy Association (HOPA) News*. 2018; 15(1). Conti R. *Biosimilars: Reimbursement Issues in Your Oncology Practice.* American Society of Clinical Oncology. Vol. 13. Sept 2017.

Financial Forecast Analysis

- System-wide product utilization by site of care
- WAC/ASP-based cost savings
- Medicare revenue analysis
  - Published payment schedule
  - Pass-through for 340B practices
- Commercial revenue analysis
  - Payer mix
  - Effective rate of payment

WAC = Wholesale Acquisition Cost, ASP = Average Selling Price

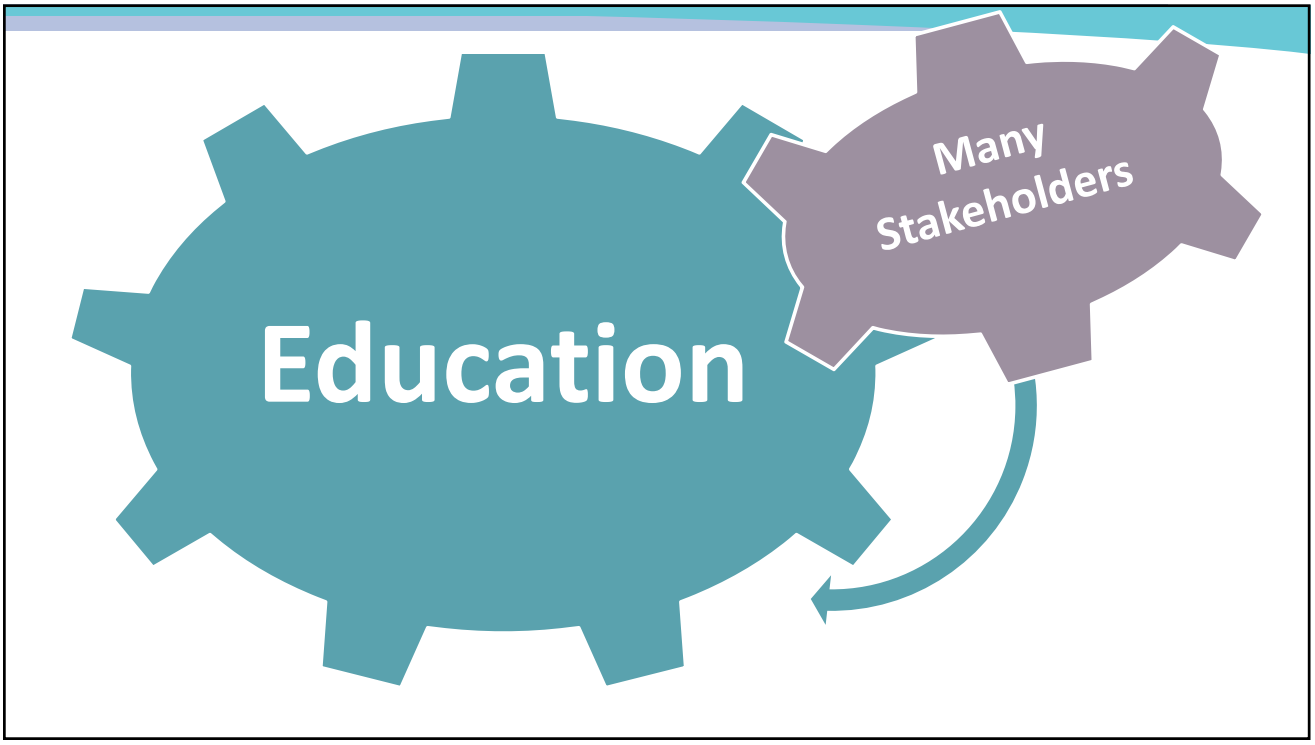
Financial Forecast Analysis

- Quality Assurance (QA)
  - Q-code
  - Wholesaler price accurately
  - Charge master (e.g., mark-up consistency, charge validation)
- Managed care impact modeling
- Retrospective forecast validation

Biosimilar Reimbursement

- Financial impact education
  - Budgeting
  - Managed care
- **CASE – Lowest cost of care provider**

Schwieterman P. A Strategic Review of Biosimilars in Oncology Practice. *Hematology/Oncology Pharmacy Association (HOPA) News*. 2018; 15(1). Conti R. *Biosimilars: Reimbursement Issues in Your Oncology Practice.* American Society of Clinical Oncology. Vol. 13. Sept 2017.



Biosimilar Education

- Significant knowledge gaps in key stakeholders

U.S. Surveys (2013-2016)

30% of oncologists perceive biosimilars **less safe** than reference counterpart due to **abbreviated regulatory** pathway

Only 12% indicate comfort with **extrapolation**

Lyman G et al. Rationale, Opportunities, and Reality of Biosimilar Medications. *N Engl J Med*. 2018; 378:2036-44.
Mehr SR et al. Factors Influencing the Economics of Biosimilars in the US. *J Medical Economics*. 2017; 20:1268-71.
Kim W et al. Looking to the Future and Learning Lessons from the Recent Past: Changing Stakeholder Perceptions of Biosimilars in Cancer. *Future Oncology*. 2017; 13(15s):17-29.

Biosimilar Education

- Significant knowledge gaps in key stakeholders

2013 survey prior to launch of first infliximab biosimilar

13% of gastroenterologists were very or totally **confident** with **safety and efficacy** compared with 47% after 2 years of experience with product

Lyman G et al. Rationale, Opportunities, and Reality of Biosimilar Medications. *N Engl J Med*. 2018; 378:2036-44.
Mehr SR et al. Factors Influencing the Economics of Biosimilars in the US. *J Medical Economics*. 2017; 20:1268-71.
Kim W et al. Looking to the Future and Learning Lessons from the Recent Past: Changing Stakeholder Perceptions of Biosimilars in Cancer. *Future Oncology*. 2017; 13(15s):17-29.

Biosimilar Education

Overall effect on healthcare cost is dependent on providers, payers, and patients' understanding of safety and efficacy

- Biosimilar regulatory approval process
- Biologic manufacturing
- Product drift
- Extrapolation
- Switching
- Immunogenicity

Lyman G et al. Rationale, Opportunities, and Reality of Biosimilar Medications. *N Engl J Med*. 2018; 378:2036-44.
Mehr S et al. Factors Influencing the Economics of Biosimilars in the US. *J Medical Economics*. 2017; 20:1268-71.
Kim W et al. Looking to the Future and Learning Lessons from the Recent Past: Changing Stakeholder Perceptions of Biosimilars in Cancer. *Future Oncology*. 2017; 13(15s):17-29.

Biosimilar Education

- Others turn to pharmacists as the expert

- Internal stakeholder education
  - Interprofessional peer education

Biosimilar Education

External Stakeholder Education

- Patients
  - Chemotherapy/ biotherapy class
  - Financial navigation

Biosimilar Education

External Stakeholder Education

- Patients

www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM595858.pdf. Accessed 3/17/2019.

Biosimilar Education

External Stakeholder Education

- Professionals – Conferences
- Public – PBS live TV

Biosimilar Education

Pharmacy and Therapeutics (P&T) Committee Evaluation

I. Educate key physician leaders

II. Bring general biosimilar education to P&T Committee

III. Introduce biosimilar product-specific monograph to P&T Committee

Biosimilar Education

I. Educate Key Physician Leaders

1. Biologic utilization trends
2. Small vs. large molecule differences
3. Goal to demonstrate biosimilarity; not to reestablish primary efficacy and safety
4. Inherent biologic variability
5. Phase III confirmatory clinical trials may not be required

Biosimilar Education

I. Educate Key Physician Leaders (Continued)

6. Pharmacovigilance
    1. Growing body of real-world clinical evidence
    2. U.S. & E.U. safety and efficacy track record
7. How biosimilars fit into inpatient and outpatient cost containment strategies

E.U. = European Union

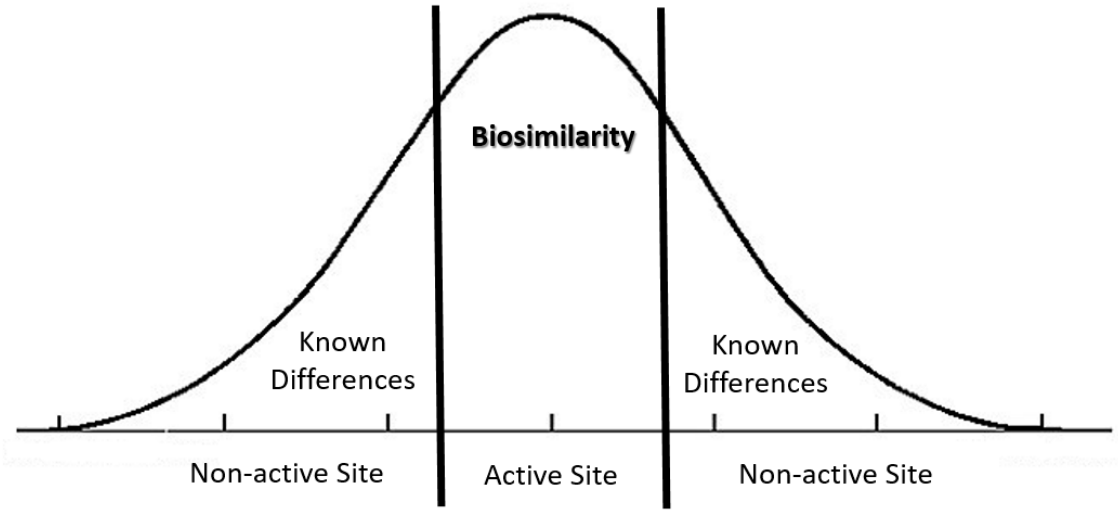
Biosimilar Education

II. P&T Committee General Biosimilar Education

1. Biosimilars scientific review
2. Value proposition
    1. Biologic utilization and cost trends
    2. Reimbursement model evolution
    3. Financial risk shift

Biosimilar Education

II. P&T Committee General Biosimilar Education

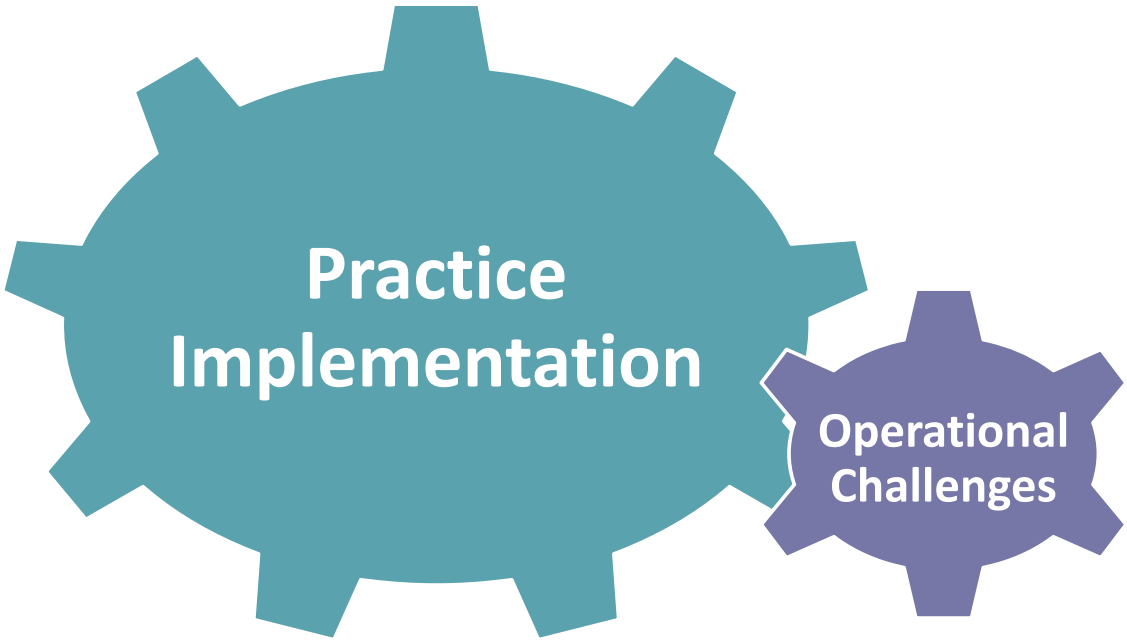


Biosimilar Education

III. P&T Committee Product Specific Biosimilar Education

- Drug monograph
- Reference primary studies
- Review biosimilar PK, PD, and immunogenicity studies
- Assess complete or near-complete indications
- Focus on any label differences
- Role of institutional drug policy to drive product substitution
  - Auto-substitution criteria

PK = Pharmacokinetics, PD = Pharmacodynamics



Operational Challenges

Pharmacy Informatics Considerations

- Resource availability
- Product build
- Treatment plan updates
- New functionality availability
- Validation

Operational Challenges

Operational Considerations

- Plan for switching patient orders
  - New vs. established patients
  - Single order vs. treatment plan
  - Route for co-signature

Operational Challenges

Operational Considerations

- Product inventory
  - Payer & facility formulary misalignment
  - "Skinny label"
  - Storage capacity
  - ADC capacity

ADC = Automated Dispensing Cabinets

Operational Challenges

Operational Considerations

- Look alike – sound alike drugs
- Interprofessional collaboration
  - Registration team

Operational Challenges

Evolution of Care Delivery

- New delivery systems
  - Pegfilgrastim on-body injector
- New Formulations
  - Rituximab and hyaluronidase
  - Trastuzumab and hyaluronidase-oysk

Operational Challenges

Evolution of Care Delivery

- Value considerations
  - Scheduling
  - Infusion volume management
  - Transportation / access / adherence
  - Revenue
  - Site of care
  - Medication adherence / outcomes

Operational Challenges

New Product Interchange Workflow

- Previous
  - Provider ordered based on preference
  - BO contacted provider when payer benefits called for different product

BO = Business Office

Operational Challenges

New Product Interchange Workflow

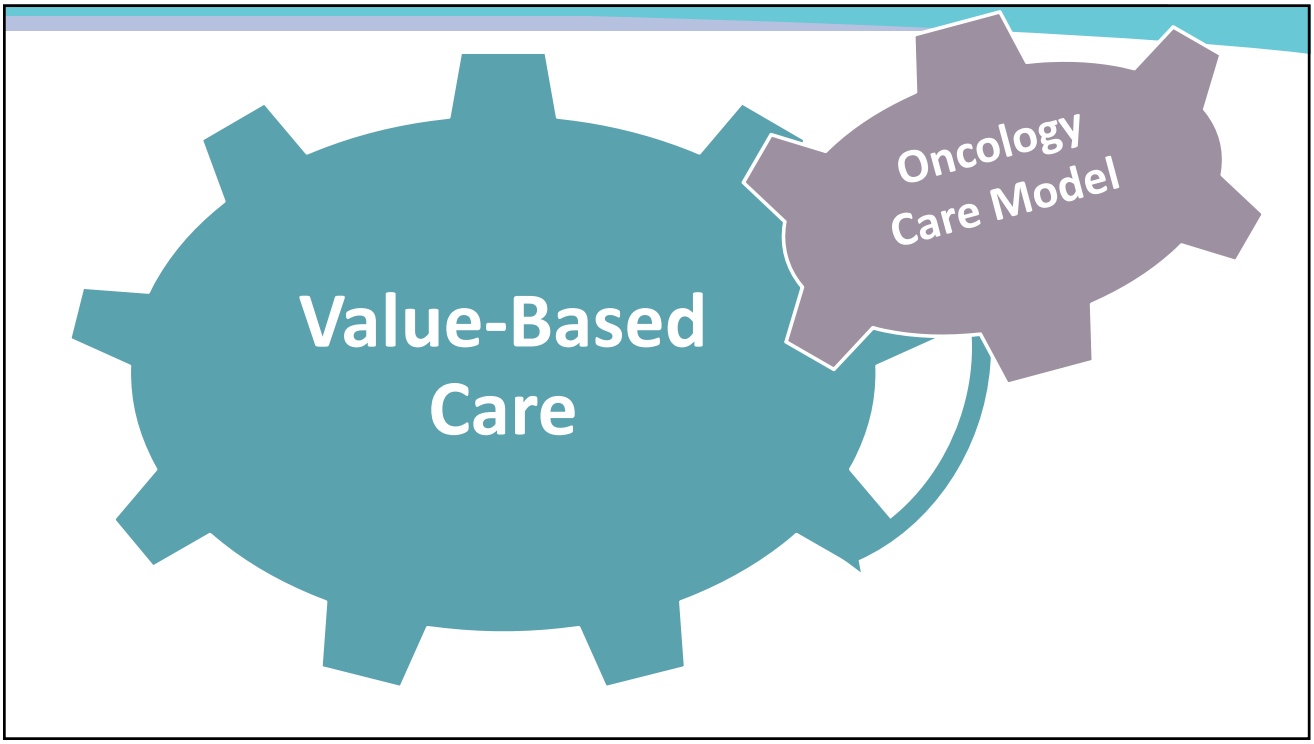
- Current
  - Provider enters generic order
  - BO conducts benefits investigation
    - Based on preferred facility tier system
    - Restricts to payer benefit if applicable
  - PA documented on EMR
  - Pharmacist leads product selection

PA = Pre-Authorization, EMR = Electronic Medical Record

Operational Challenges

New Product Interchange Workflow – Advantages

- Provider satisfaction
- BO satisfaction
- Pharmacy leads product utilization
- Positioned for success
  - Increasing number of biosimilars
  - Increasing number of reference formulations



Biosimilars in Value-Based Care Models

Fee-for-Service | Shared Savings | Bundled Payment | Partial Capitation | Full Risk

- Increasing number of providers working in Accountable Care Organizations (ACOs) and "narrow networks"
- University of Pittsburgh Medical Center (UPMC) / Highmark - Allegheny Health System / Kaiser
- Self-insured Employee Health Plans

Lawless G. Overcoming Challenges in the Emerging Biosimilar Landscape. *J Managed Care Medicine*. 2017; 20(4).

Biosimilars in Value-Based Care Models

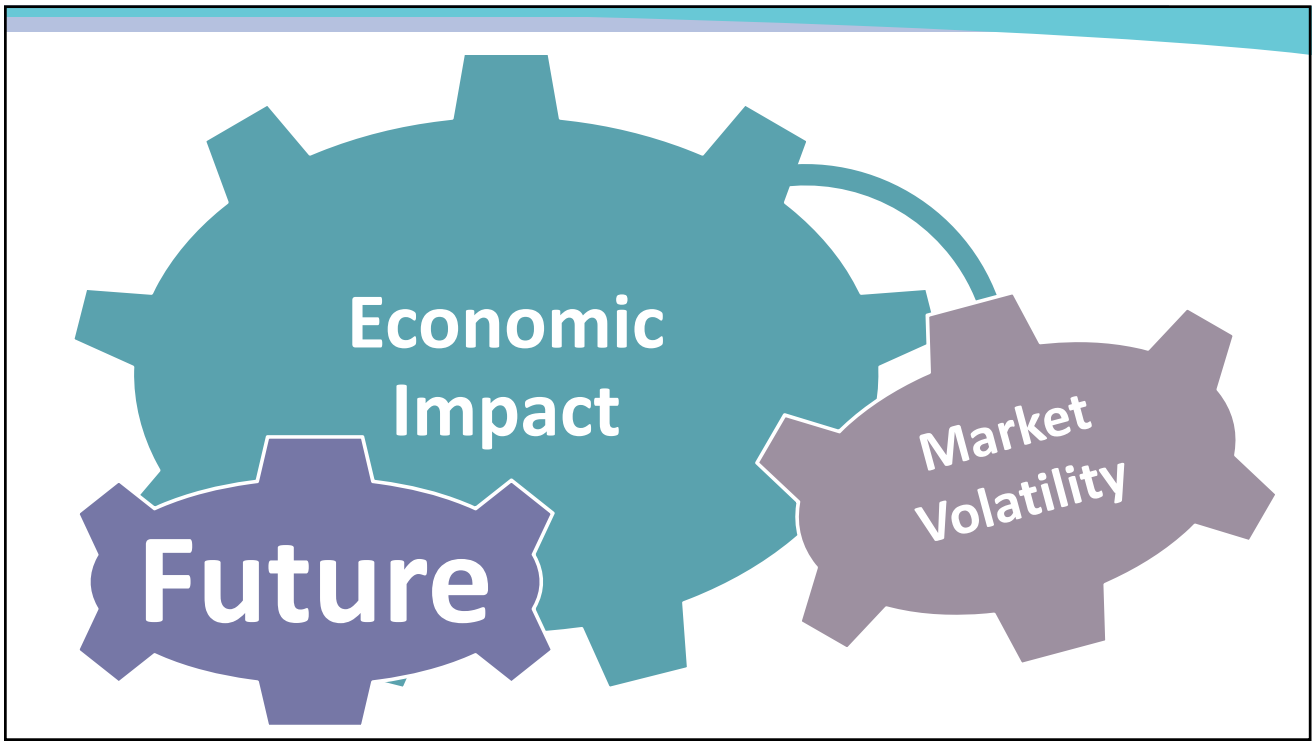
- Disproportionately greater elderly population in oncology
- Cost mitigation strategies
  - Incentivizing high quality
  - Payment increasingly tied to performance
  - Risk shift

Biosimilars in Value-Based Care Models

Oncology Care Model (OCM) (launched June 2016)

- Voluntary, two-sided risk model
- Better care coordination
- Quality metrics and practice reforms
- Lower cost than traditional Medicare FFS
- 192 practices & 14 commercial plans participating
- Drug budget management

FFS = Fee for Service



Market Uncertainty

CASE - Market Risks and Opportunities

Biosimilars Current State of Affairs

- 25 biosimilars FDA approved in U.S.*
  - Less than half in the market
  - Less than 2% of total U.S. biologics market
- 62 biosimilars for sale in E.U.*
  - Providing alternatives to >70% of all biologic therapies
- International biosimilar sales
  - >87% spending in E.U.
  - 2% spending in U.S.

*As of Nov 2019

Schwieterman P. A Strategic Review of Biosimilars in Oncology Practice. *Hematology/Oncology Pharmacy Association (HOPA) News*. 2018; 15(1).

Biosimilar Economic Impact in U.S.

- Biosimilars expected to enter market at 15-30% discount from reference product
- Potential reference product net price reduction:
  - filgrastim – 30%
  - infliximab – 30%

Nabhan C et al. Barriers to Oncology Biosimilars Uptake in the United States. *The Oncologist*. 2018; 23:1261-65.
Lawless G. Overcoming Challenges in the Emerging Biosimilar Landscape. *J Managed Care Medicine*. 2017; 20(4).

Biosimilar Economic Impact in U.S.

- Discount variation:
  - Manufacturer quality
  - Manufacturer location and ability to provide uninterrupted supply
  - Support services
  - Managed care contracting
  - Order of market entry

Nabhan C et al. Barriers to Oncology Biosimilars Uptake in the United States. *The Oncologist*. 2018; 23:1261-65.
Lawless G. Overcoming Challenges in the Emerging Biosimilar Landscape. *J Managed Care Medicine*. 2017; 20(4).

Biosimilar Economic Impact in U.S.

- Driving further price competition once in market
  - Multiple biosimilars per reference product
  - Discounts settlement may take up to a decade
  - Is early biosimilar adoption a sound strategy?

Nabhan C et al. Barriers to Oncology Biosimilars Uptake in the United States. *The Oncologist*. 2018; 23:1261-65.
Lawless G. Overcoming Challenges in the Emerging Biosimilar Landscape. *J Managed Care Medicine*. 2017; 20(4).

Biosimilar Economic Impact in E.U.

- Europe has achieved mean price discounts ranging from 15-40%
  - 39% in France
  - 55% in Germany
  - Highest number of approved biosimilars worldwide

Nabhan C et al. Barriers to Oncology Biosimilars Uptake in the United States. *The Oncologist*. 2018; 23:1261-65.
Lawless G. Overcoming Challenges in the Emerging Biosimilar Landscape. *J Managed Care Medicine*. 2017; 20(4).

Biosimilar Economic Impact in U.S.

- Patent Expirations:
  - Cetuximab – 2014
  - Rituximab – 2016
  - Bevacizumab – 2019
  - Trastuzumab – 2019
  - "heavy dent in oncology cost curve"

Patel KB et al. *The Role of Biosimilars in Value-based Oncology Care.* Dovepress. October 2018. Mehr SR et al. Factors Influencing the Economics of Biosimilars in the US. *J Medical Economics*. 2017; 20:1268-71. Kelley T. Biosimilars in Oncology: Reality Could Bite the Copycats, Dog Potential Major Savings. *Drug Management*. MediMedia. March 12, 2017.

Biosimilar Economic Impact in U.S.

- Overall economic impact difficult to assess
  - Limited experience
  - Many variables
- RAND Corporation predicts cumulative $44.2 billion in savings from 2014-2024
- Express Scripts estimates $250 billion in savings by 2024
  - Infliximab & filgrastim accounting for $22 billion

Patel KB et al. *The Role of Biosimilars in Value-based Oncology Care.* Dovepress. October 2018. Mehr SR et al. Factors Influencing the Economics of Biosimilars in the US. *J Medical Economics*. 2017; 20:1268-71. Kelley T. Biosimilars in Oncology: Reality Could Bite the Copycats, Dog Potential Major Savings. *Drug Management*. MediMedia. March 12, 2017.

Biosimilar Advocacy

- Providers are an important and influential stakeholder
- Payer policy
  - At-parity formulary position
- Provider/patient choice
- Managed care contracts
  - Arm your team to leverage contract
- Sustainable biosimilar model
  - Trickle down economics

Summary

- Biologics have revolutionized the treatment of serious conditions in the past 20 years
- Biologics increased utilization and cost have provided a call for action
- High barriers to entry remain in biosimilar market
- Biosimilars are uniquely positioned to perform under value-based care and at-risk models

Summary

Unsustainable healthcare costs remain a key public concern

Biosimilars offer a viable avenue to reduce healthcare spending

Providers have a responsibility to evaluate and ensure the safe and effective use of biosimilars

Pharmacists are uniquely positioned to LEAD the effort

Consider these practice changes. Which will you make?

- Educate other healthcare providers about biosimilars and their effective use.
- Educate patients with cancer about the appropriate, effective, and safe use of available biosimilars.
- Discuss with colleagues the logistical considerations for incorporating biosimilars at my organization.
- Lead efforts to operationalize the use of biosimilars in my organization.
- Recommend biologics/biosimilars to other healthcare providers for patients with applicable cancers.
- Discuss with colleagues the transition from originator products to biosimilars to guide the treatment of patients with applicable cancers.

Q & A

About the Faculty

Sandra Cuellar, Pharm.D., BCOP
Clinical Oncology Pharmacist
University of Illinois Hospital and Health Sciences System
Associate Professor
University of Illinois at Chicago College of Pharmacy
Chicago, Illinois

Sandra Cuellar, Pharm.D., BCOP, is Clinical Associate Professor in the Department of Pharmacy Practice at the University of Illinois at Chicago (UIC) College of Pharmacy and clinical oncology pharmacist in the ambulatory cancer center at the University of Illinois Hospital and Health Sciences System. She currently is vice chair of the institutional review board (IRB), director of the PGY-2 oncology residency, and team leader for oncology pharmacy.

Dr. Cuellar received her Bachelor of Liberal Arts from Augustana College in Rock Island, Illinois, followed by her Doctor of Pharmacy from the UIC College of Pharmacy. She then completed a Pharmacy Practice Residency at University of Kentucky Chandler Medical Center. Following her residency, she completed a specialty oncology residency at MD Anderson Cancer Center in Houston, Texas.

Dr. Cuellar has been active in the field of hematology/oncology for 17 years. She is an editor at large for the *Journal of Hematology Oncology Pharmacy* and is involved in research, consulting, and publications in the field of hematology/oncology. Dr. Cuellar has served in leadership positions in the American Society of Health-System Pharmacists (ASHP) and the Hematology/Oncology Pharmacy Association (HOPA).

Jorge J. García, Pharm.D., M.S., M.H.A., M.B.A., FACHE
Assistant Vice President—Pharmacy
Baptist Health South Florida
Miami Cancer Institute—Lynn Cancer Institute
Miami, Florida

Jorge J. García serves as an Assistant Vice President at Baptist Health South Florida with responsibility for system-wide oncology pharmacy services primarily at the Miami Cancer Institute, the Lynn Cancer Institute, and inpatient oncology pharmacy services at several acute hospitals in the system. Dr. García has pioneered pharmacy charge integrity and revenue management in the health-system setting and is a thought leader and national speaker in this area, as well as in the areas of alternative payment models, biosimilars, and value-based oncology care. Dr. García leads advocacy efforts at the national level to promote evaluation of safe and effective use of biosimilars, along with stakeholders' engagement to support a more sustainable biosimilar pharmacoeconomic model.

Dr. García obtained his Doctor of Pharmacy and M.B.A. from Nova Southeastern University in 2010. Dr. García then transitioned to the University of Pittsburgh Medical Center to pursue an ASHP-accredited PGY-1 & PGY-2 Health-System Pharmacy Administration Residency and a Master of Science in Pharmacy Administration. He also completed an M.H.A. from Florida Atlantic University.

Dr. García is a board member at Florida Society of Clinical Oncology (FLASCO) and also the recipient of the FLASCO 2018 Above and Beyond Award. Dr. García is a fellow of the American College of Healthcare Executives (ACHE).

Release date: February 18, 2020
Expiration date: May 19, 2021

ADDITIONAL ACTIVITIES ON BIOSIMILARS

■ On-demand follow-up activities coming in Spring 2020

www.ashpadvantage.com/biosimilarsinoncology

ACCREDITATION

The American Society of Health-System Pharmacists (ASHP) is accredited by theAccreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

ACPE #0204-0000-19-425-H01-P
1.5 contact hours, application-based