PHARMACOECONOMICS OF BIOLOGICS & BIOSIMILARS

ESSENTIALS FOR PHARMACISTS

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DISCLOSURE

Consultant to DataMed Solutions, LLC (Have assisted that company in providing contract research services to Novartis Pharmaceuticals and Gilead Sciences)

Learning Objectives

Pharmacist Learning Objectives:

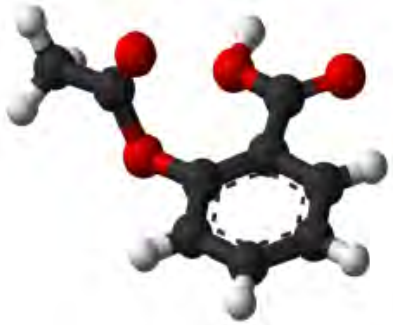
- Explain factors that have propelled biologics to currently account for a dominant proportion of prescription drug spending.
- Describe methods used in the US and other countries to estimate comparative value of biologics vs. traditional pharmaceuticals.
- Discuss key economic issues that have led to a much slower uptake of biosimilars in the US vs other countries and recent US advances in the expected approval rate and market introduction of biosimilars.
- Understand the expressed knowledge gaps of prescribers and other health professionals related to comparative cost and patient access to biologics and biosimilars.
- Describe reported incentives and disincentives that have influenced biosimilar uptake.

BIOLOGICS

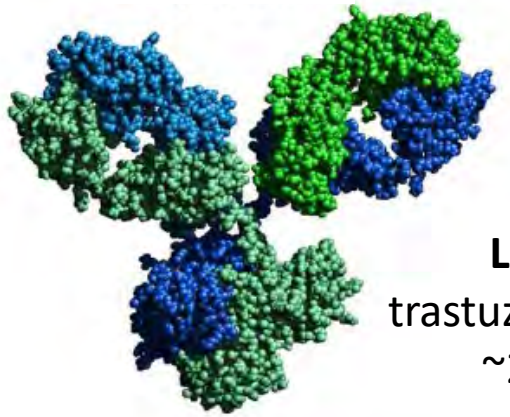
Rise of Biologics

Recombinant Human Insulin (1982)

Small Molecule Drug/ Pharmaceutical
Aspirin
21 atoms



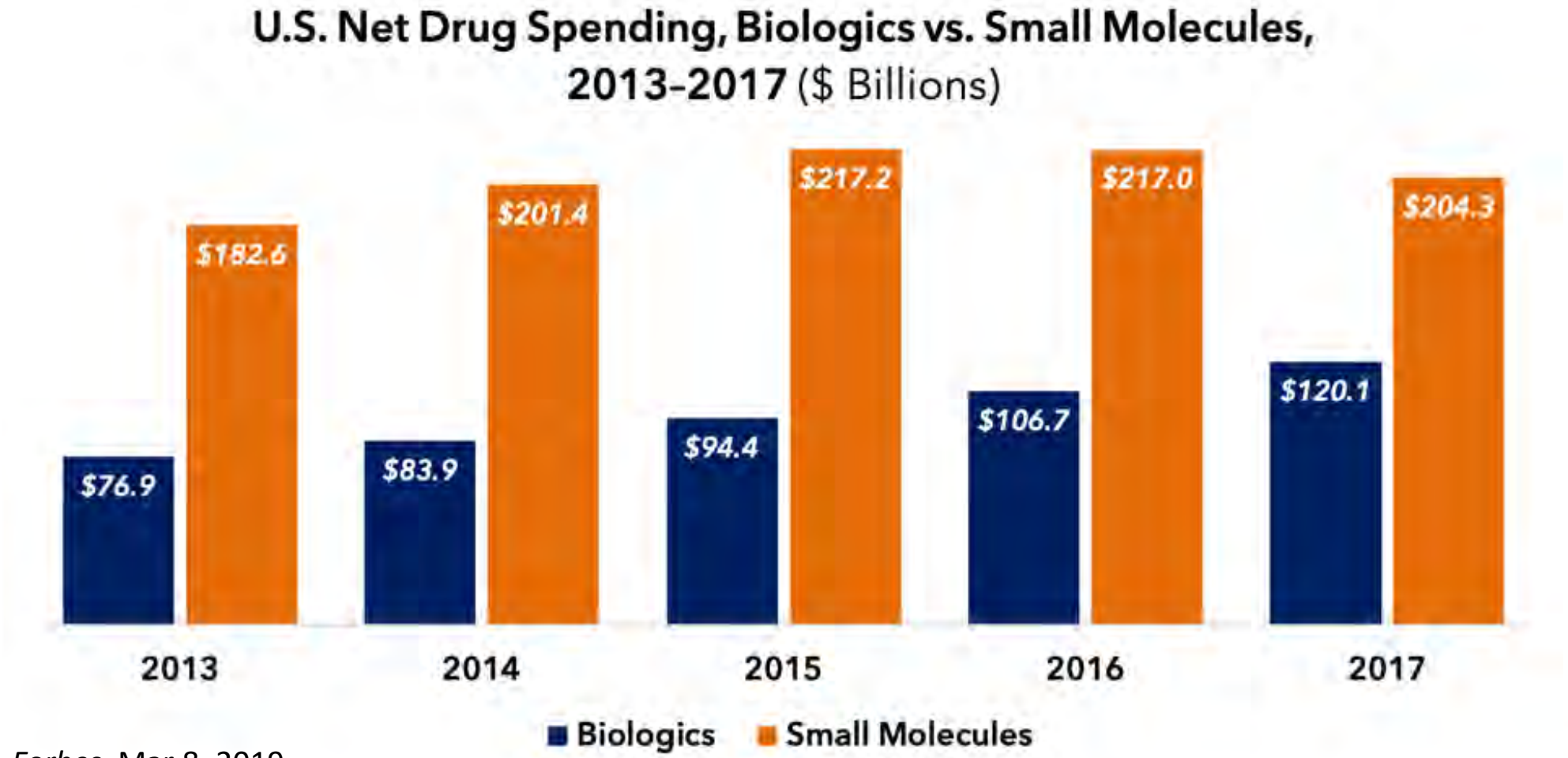
Large Molecule Drug
Human Growth Hormone
~3,000 atoms



Large Biologic
trastuzumab (Herceptin)
~25,000 atoms

1. National Museum of American History.
2. Smith A. Edison *Investment Research*. Jun 18, 2019.

TREND OF SPEND



3. Roy A. *Forbes*. Mar 8, 2019.

Breakthroughs and Busted Budgets

- Introductions between 2012 and 2014:
  - sofosbuvir (Sovaldi) and ledipasvir/sofosbuvir (Harvoni) for hepatitis C
  - ivacaftor (Kalydeco) for cystic fibrosis
  - teduglutide (Gattex) for short-bowel syndrome
- Medicare expenditures for hepatitis C drugs increased from $300 million in 2013 to $4.5 billion in 2014.
- Medicare Part D (drug coverage) catastrophic spending increased by 363% over the previous eight years to nearly $28 billion in 2014.

4. Ornstein C. *ProPublica*. Mar 29, 2015.
5. Alexander GC, Ballreich J, Socal MP, et al. *Pharmacotherapy*. 2017.

WHY ARE BIOLOGICS EXPENSIVE?

1. Growing affluence
2. Capital investments required
3. Multi-sided markets
4. Pricing that considers expected savings from costs of care
5. Persistence of asserted intellectual property claims

ARE WE TRADING HIGH BENEFITS FOR HIGH COSTS?

- For many progressive conditions, biologics offer the *potential* for significant and meaningful gains in quality adjusted life years.

- Typically, biologics cost substantially more than small-molecule therapies.

Impact of Costs on Patients

- In one study, median out-of-pocket patient costs for Medicare Part D enrollees was estimated at $4,413 to $11,538 across 12 biologics.
  - Patients today must pay $6,350 in out-of-pocket drug costs before reaching catastrophic coverage, then pay 5% of drug plan's negotiated drug cost.
- In one review, economic factors (such as patient-borne expenses) were associated with non-adherence of biologics among rheumatoid arthritis patients.
  - The proportion of patients deemed adherent to biologics was as low as 11%.

6. Hoadley J & Neuman T. It Pays to Shop. 2015.
7. De Vera MA, Mailman J, Galo JS. *Current Rheumatology Reports*. 2014.

Comparative Value and Biologics

- Value-based pricing (VBP) is a promising strategy for payment of biologics, yet remains challenging to execute.
  - VBP emphasizes higher payments for better outcomes in actual care settings.
- Health Technology Assessement (HTA) is currently a more viable alternative, with a long experience in many countries.
- Use of cost-effectiveness in making product coverage decisions remains limited in the United States:

Most restrictive → *Least restrictive*

Australia → Canada → France → United Kingdom → United States

8. Zhang Y, Hueser HC, Hernandez I. *J Managed Care Specialty Pharmacy*. 2017.

U.S. System vs Other Countries

- The U.S. has the highest per capita spending on prescription drugs and tends to introduce new drugs to market faster and with higher utilization rates.
- Among the 34-member Organisation for Economic Cooperation and Development (OECD), the U.S. is the only country without significant government oversight or regulation of prescription drug pricing.
- The Affordable Care Act restricts the government-supported Patient-Centered Outcomes Research Institute (PCORI) from reporting quality-adjusted life years (QALYs) in sponsored research publications.
- The Institute for Clinical and Economic Review (ICER) is an independent entity attempting to establish cost-effectiveness benchmarks.

9. Daniel H. *Ann Intern Med*. 2016.
10. Institute for Clinical and Economic Review (ICER).

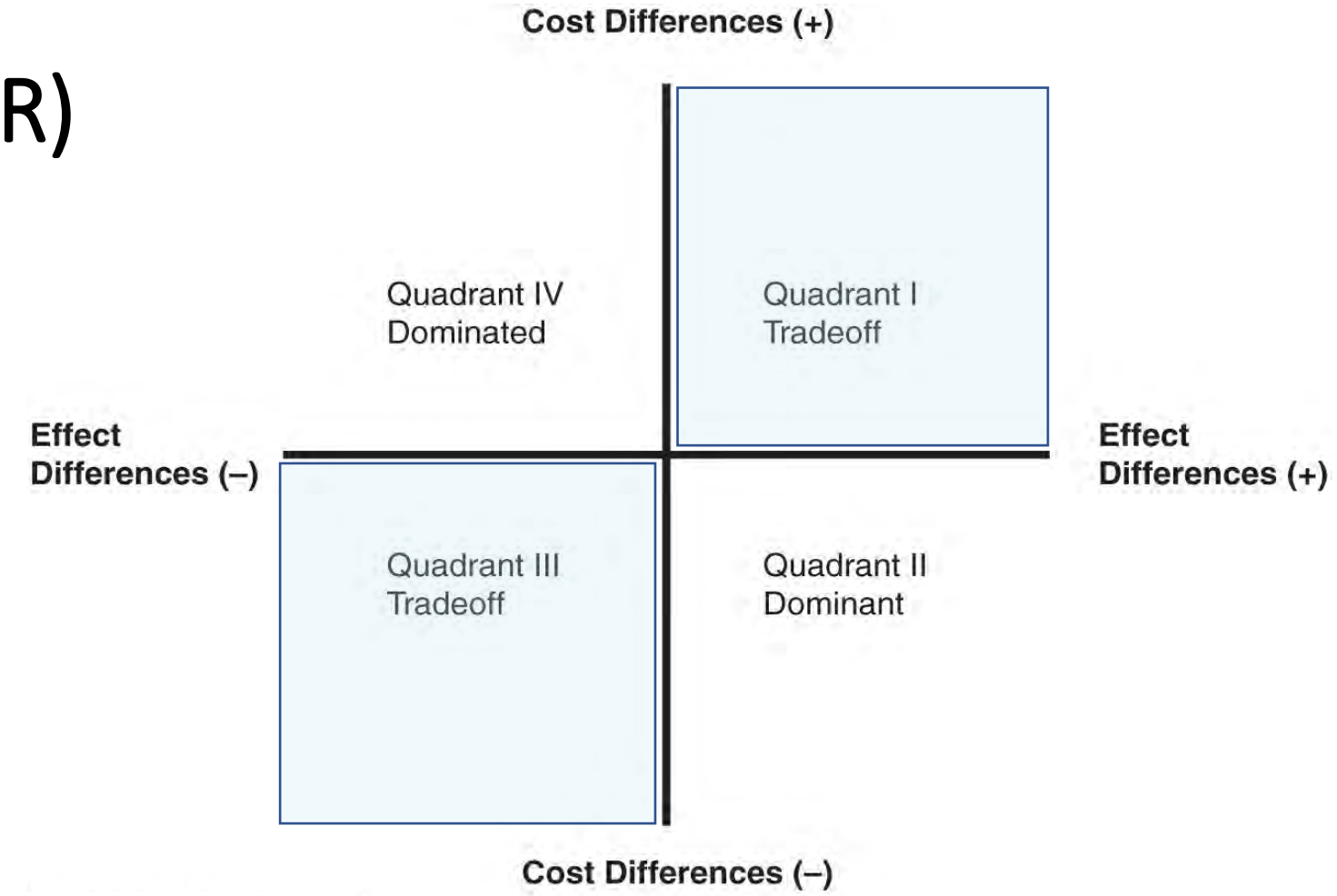
WILL THE U.S. BREAK TOWARD HTA FOR BIOLOGICS?

- One consequence of high spending on biologics is calls for changes to payer practices.
- Examples of professional associations that have issued statements in support of legislative or regulatory solutions to improve payer control of high drug costs include:
  - American College of Physicians (ACP)
  - American Society of Clinical Oncology (ASCO)
  - American Heart Association (AHA)

9. Daniel H. *Ann Intern Med*. 2016.
11. Antman EM, Creager MA, Houser SR, et al. *Circulation* 2017.
12. ASCO. *J Oncology Practice*. 2018.

Incremental Cost-Effectiveness Ratio (ICER)

$$\frac{Cost_{\ Comparator} - Cost_{\ Referent}}{Effect_{\ Comparator} - Effect_{\ Referent}}$$



13. Rascati KL. Pharmacoeconomics, 2013.

VALUE OF INNOVATOR BIOLOGICS

In one study, incremental costs per QALY (also known as incremental cost-effectiveness ratios or ICERs) were calculated for biologics and traditional drugs.

- Specialty drugs were associated with greater incremental costs (vs. pre-existing care) compared to traditional drugs (median $12,238 vs $784).
- But specialty drugs had larger QALY gains (median 0.183 vs 0.002 QALYs).
- Both drug types had comparable cost-effectiveness vs. pre-existing care.

ICERs for biologics versus routine care often vary widely by product.

- One review of treatments for ulcerative colitis showed ICERs ranging from $36,309 to $456,979 per QALY gained.

14. Chambers JS, Thorat T, Pyo J. *Health Affairs*. 2014.
15. Stawowczyk E & Kawalec P. *PharmacoEconomics*. 2018.

VALUE OF INNOVATOR BIOLOGICS

Without the cure offered by recent biologics, 350,000 more patients in the US would have been living with advanced stages of hepatitis C between 2015 and 2025, at a burden of illness cost of $115 billion.

Still to be resolved is the estimated three million persons in the U.S. with hepatitis not yet treated with a biologic.

9. Daniel H. *Ann Intern Med*. 2016.
16. Pyenson B, Bochner A, Cannon R. An Actuarial Approach. 2015

Cost of Developing Biologics

- This is not known for biologics.
  - The most-cited statistic for *any new pharmaceutical* is $2.6 billion, including a $1.4 billion cash outlay and $1.2 billion in opportunity costs of capital.
- Time-to-payback for most biologics is likely to be quick.
- Sales of the top 20 biologics generated median annual sales of $3.73 billion in 2018, ranging from $2.6 billion (emtricitabine/tenofovir disoproxil fumarate [Truvada]) to $13.7 billion (adalimumab [Humira]).
  - Ex-U.S. sales added another 50% in additional revenues for adalimumab.

17. DiMasi JA, Grabowski HG, Hansen RW. *J Health Econ*. 2016.
18. Blankenship K. *FiercePharma*. Jun 17 2019.

TEST QUESTION #1

The independent entity that is attempting to establish cost-effectiveness benchmarks in the US is known as _____.

A. Academy of Managed Care Pharmacy

B. Food and Drug Administration

C. Institute for Clinical and Economic Review

D. National Institute for Health and Care Excellence

BIOSIMILARS

BIOSIMILARS IN EUROPE

- A biosimilars pathway was fully enacted in 2006.
  - 54 biosimilars have been approved for use by the European Medicines Agency, as of October 2019.
- Policies enforcing uptake of biosimilars in some European countries have been strong.
- Decentralization of health care budgets and issuance of local guidelines results in substantial variance by region.

19. Generics and Biosimilars Initiative. Oct 25, 2019.

BIOSIMILARS IN THE U.S.

- Biologics Price Competition and Innovation Act (BPCIA) created a pathway for biosimilars in 2010.
- FDA has approved 24 biosimilars (vs. 54 in Europe), but only 11 products have been launched to market, as of 2019.
- Rand Corporation estimated biosimilars would result in a $44 billion reduction in biologic spending from 2014 to 2024.
  - Realized savings have been far less.
  - Biosimilars in 2018 had penetrated less than 0.8% of the U.S. market for biologics.

20. Cohen J. *Forbes*. Jul 11 2019.
21. Singh SC & Bagnato KM. *Am J Managed Care*. 2015.
22. Manolis CH, Rajasenan K, Harwin W, et al. *J Managed Care Spec Pharmacy*. 2016.
23. Aitken M & Kleinrock M. Medicine Use and Spending in the U.S. May 2019.

PRODUCT DISCOUNTS IN U.S. VS. EUROPE

- U.S.: Biosimilar product discounts of 15% to 35% below the originator price have been reported.
- Europe: Biosimilar discounts have been reported, ranging from 5% to 75% below originator price.

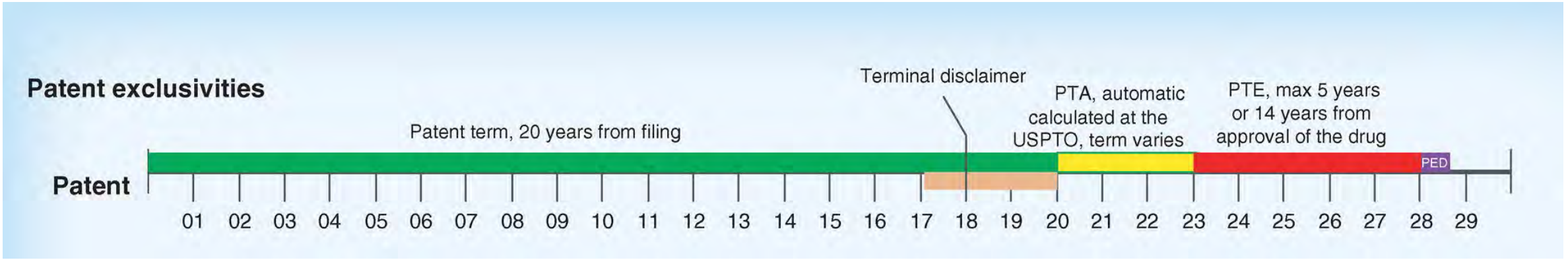
20. Cohen J. *Forbes*. Jul 11 2019.
24. Blackwell K, Gligorov J, Jacobs I, et al. *Clin Breast Cancer*. 2018

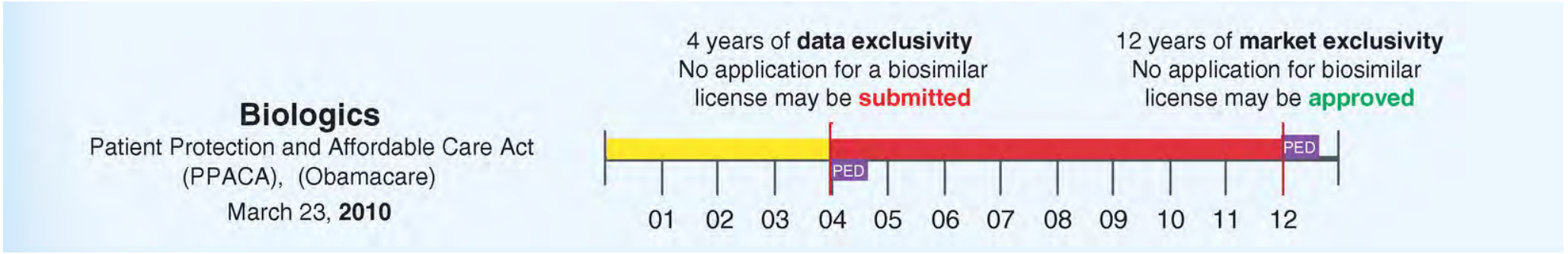
Data Exclusivity and Patent Battles

- Product approval can produce an uncertain outcome for a biosimilar manufacturer.
  - 6 of 12 biosimilars approved for marketing by the FDA were held back from commercial launch due to “marginally inventive” patent disputes with the originator.
- Example of delays for biosimilar launch resulting from patent disputes:
  - etanercept (Enbrel) until 2029

25. Chen BK, Yang YT, Bennett CL. *Drugs*. 2018.
26. I-MAK. Overpatented, Overpriced. 2018.

PATENT PROTECTION VS DATA EXCLUSIVITY





Terms: Patent Term Adjustment (PTA); Patent Term Extension (PTE); Pediatric Exclusivity (PED; United States Patent and Trademark Office (USPTO)

27. Peng B & Cavero Tomas M. *Pharmaceutical Patent Analyst*. Oct 7, 2014.

PATENT DANCE

- BPCIA has a two-step process (termed “patent dance”) for patent approval
  - 1st step: An informational patent disclosure or “exchange” between a biosimilar candidate and the originator is triggered by acceptance of the biosimilar application by the FDA.
    - Includes negotiations regarding which patents may be asserted or challenged as patent infringement.
  - 2nd step: Litigation of disputed patents.
    - Reluctance of the originator to fully comply with the exchange provision might slow biosimilar development.

28. Ha CY & Kornbluth A. *Inflammatory Bowel Diseases*. 2016.
29. Frank RG. *NEJM*. 2018.

OTHER CONTROLS

- "Pay for delay"
  - Example: Deal reached by AbbVie with Samsung Bioepis and Biogen
    - Launch of South Korean biosimilar to adalimumab (Humira) to the U.S. market was delayed until 2023 per agreement between manufacturers.
- Rebate matching
  - Discounts, such as 15% to 35% below the originator's price, as offered by recent biosimilar manufacturers, might be easily matched by an originator manufacturer.

30. Barlas S. *P&T*. 2019.
20. Cohen J. *Forbes*. Jul 11 2019.

OTHER CONTROLS

- "Rebate trap"
  - Originator manufacturer responds to a successful challenge by a biosimilar manufacturer for a payer or institution's preferred formulary listing by contractually withdrawing the rebate on its product.
    - Difficult for institutions or payers to shift more than a minority of patients from a given originator biologic to a biosimilar.
    - For all patients continuing on the originator biologic, the payer's costs for that patient could double after the rebate is withdrawn.

31. Hakim A & Ross JS. *JAMA*. 2017.

TEST QUESTION #2

A biologic manufacturer threatens to withdraw the rebate on its reference biologic for a payer who plans to place a biosimilar substitute on its formulary. This might trigger the _____.

A. Patent dance

B. Abbreviated new drug application

C. Pay for delay

D. Rebate trap

PROVIDER KNOWLEDGE OF AND ATTITUDES TOWARD BIOSIMILARS

Both US and European health care providers have cited several deterrents for biosimilar uptake:

- Limited prescriber knowledge of biosimilars
- Low prescribing comfort
  - Biosimilar medicines are often perceived as 2nd or 3rd-line treatment options.
  - Concerns about switching patients who already tolerate originator therapies
- Key concerns about biosimilars
  - Immunogenicity and efficacy equivalence
  - Long-term tolerability
  - Indications extrapolation

32. Leonard E, Wascovich M, Oskouei S, et al. *J Managed Care Spec Pharmacy*. 2019.

PROVIDER COMFORT WITH BIOSIMILARS: UNITED KINGDOM VS U.S.

- Recent study from the UK:
  - Prescribers had good knowledge of and were comfortable using biosimilars.
    - Increased prescribing found if departments shared in the savings, e.g. used savings to provide extra biologic nursing support
- In contrast, a recent study of U.S. oncologists found that understanding of biosimilars is low and educational needs are high.
  - Before being comfortable about prescribing biosimilars, oncologists want information regarding safety, efficacy, and cost.

33. Aladul MI, Fitzpatrick RW, Chapman SR. *BMJ Open*. 2018.
34. Cook JW, McGrath MK, Dixon MD, et al. *Therapeutic Advances Med Oncology*. 2019.

INTERCHANGEABILITY

- Substitution laws for small-molecule oral generics do not apply to biosimilars.
- Under BPCIA, substitution of a biologic without physician authorization requires that a biosimilar be specially designated with the statutory term "interchangeable."
  - FDA guidance (2019) creates more clarity for obtaining the interchangeable status.
    - Substitution of a biosimilar for its reference biologic without prescriber's expressed authorization would then be allowed by feds.

35. Conti RM. J *Oncology Practice*. 2017.
36. US FDA. Considerations in Demonstrating Interchangability. May 2019.

INTERCHANGEABILITY

- Obstacles blocking substitution without prescriber's authorization
  - Prescribers' concerns about being excluded from the decision
  - Some state laws may prohibit unauthorized interchange.
  - Pharmacist concerns for liability until regulations and professional standards evolve
  - Payers might restrict this practice.

NON-MEDICAL SWITCHING (NMS)

- Physicians might choose to initiate either an originator biologic or a biosimilar in "treatment-naïve" patients.
  - Patients who started with the originator biologic may be switched to a biosimilar at a later time.
  - Switching to biosimilars among stable originator users is described as NMS.
- Effect on Costs
  - Expected product cost savings due to lower net cost of biosimilar vs. originator
  - Would need to factor incremental costs after NMS to verify adherence or patient outcomes on the switched therapy, including pharmacovigilance monitoring.
  - Cost modeling data in the U.S. is limited to evaluate the effect of NMS.

"NOCEBO" EFFECT

- Incitement or worsening of symptoms due to physician or patient's negative attitude toward required biosimilar substitution in NMS.
- Efforts to overcome include:
  - Positive framing based on presentation of timely evidence
  - Provider and patient education
  - Institution-wide managed switching programs
  - Reimbursement of biosimilars for only newly-diagnosed patients, using:
    - Product-listing agreements for a biosimilar that compensates the payer or institution for managing uncertainty
    - Tiered co-payments or other patient incentives to promote biosimilar use

37. Kristensen LE, Alten R, Puig L. et al. *BioDrugs*. 2018.
38. Husereau D, Feagan B, Selya-Hammer C. *Applied Health Econ Health Policy*. 2018

INDICATION EXTRAPOLATION

- Approval of a biosimilar for use in an indication held by the reference product that has not been studied in comparative clinical trials of the biosimilar.
  - **FDA *position***: A biosimilar product may be approved for an indication without direct studies of the biosimilar in that indication.
    - **Provided** that total evidence in the biosimilar application supports a demonstration of biosimilarity for at least one of the reference product's indications.
- Payers and providers have expressed concerns where indications of the reference product are extrapolated to the biosimilar product, without clinical trial evidence.
  - Might affect the ability to optimize savings associated with biosimilar substitution.

22. Manolis CH, Rajasenan K, Harwin W, et al. *J Managed Care Spec Pharmacy*. 2016.
32. Leonard E, Wascovich M, Oskouei S, et al. *J Managed Care Spec Pharmacy*. 2019.
39. US FDA. Biosimilar Development. Oct 20, 2018.

TEST QUESTION #3

A patient is convinced that his psoriasis is worsening due to the substitution of a perceived inferior, but FDA-approved, biosimilar for the originator biologic he had been receiving. This best describes the _____ effect.

A. Immunogenecity

B. Nocebo

C. Interchange

D. Indication extrapolation

INCENTIVES FOR BIOSIMILAR ADOPTION

ALL ARE KEY AREAS FOR PHARMACIST INVOLVEMENT

1. Institutional policies that encourage biosimilar usage
2. Prescriber and patient education that balances negative attitudes or marketing about biosimilars
3. Continuing professional education courses on biologics and biosimilars
4. A continuous focus on outcomes, adherence and costs
5. Stakeholder communication and alignment of incentives
6. Improvement in payment formulas that incentivize biosimilar prescribing

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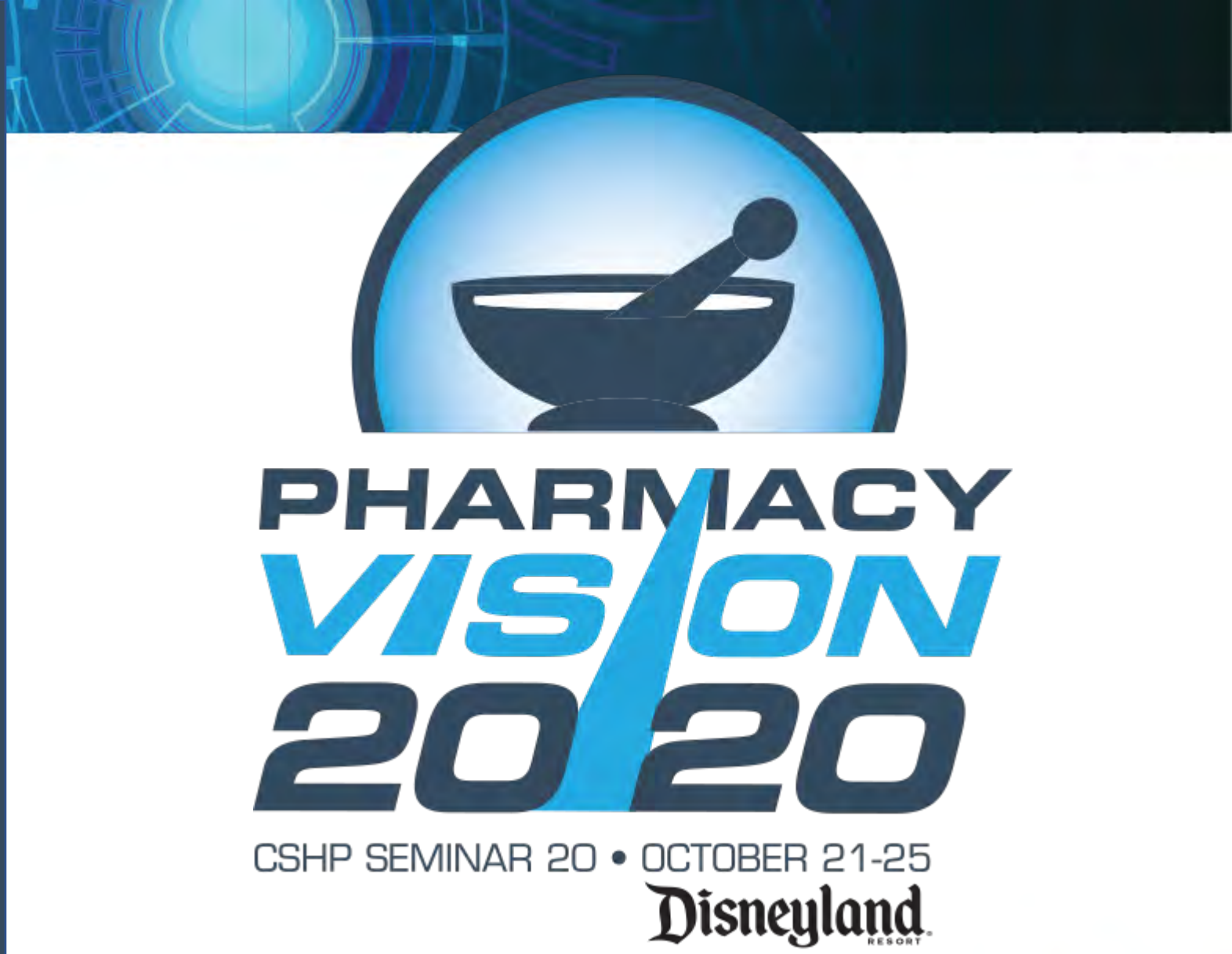

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Reference List

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6. Hoadley J, J. C, Nueman T. It Pays to Shop: Variation in Out-of-Pocket Costs for Medicare Part D Enrollees in 2016. Washington, DC, USA: The Henry J. Kaiser Family Foundation; Dec 2015.
7. De Vera MA, Mailman J, Galo JS. Economics of non-adherence to biologic therapies in rheumatoid arthritis. Current Rheumatology Reports. 2014;16(11):460.
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9. Daniel H, Health, Public Policy Committee of the American College of P. Stemming the Escalating Cost of Prescription Drugs: A Position Paper of the American College of Physicians. Ann Intern Med. 2016.
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11. Antman EM, Creager MA, Houser SR, Warner JJ, Konig M, American Heart A. American Heart Association Principles on the Accessibility and Affordability of Drugs and Biologics: A Presidential Advisory From the American Heart Association. Circulation. 2017;136(24):e441-e7.

12. American Society of Clinical Oncology. American Society of Clinical Oncology Position Statement on Addressing the Affordability of Cancer Drugs. Journal of Oncology Practice. 2018;14(3):187-92.

13. Rascati KL. Essential of Pharmacoeconomics (2nd ed.). Lippincott Williams & Wilkins, 2013.

14. Chambers JD, Thorat T, Pyo J, Chenoweth M, Neumann PJ. Despite high costs, specialty drugs may offer value for money comparable to that of traditional drugs. Health Affairs. 2014;33(10):1751-60.

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29. Frank RG. Friction in the Path to Use of Biosimilar Drugs. The New England Journal of Medicine. 2018;378(9):791-3.

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33. Aladul MI, Fitzpatrick RW, Chapman SR. Healthcare professionals' perceptions and perspectives on biosimilar medicines and the barriers and facilitators to their prescribing in UK: a qualitative study. BMJ Open. 2018;8(11):e023603.

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