JULY/AUGUST 2018 VOL. 4, NO. 4

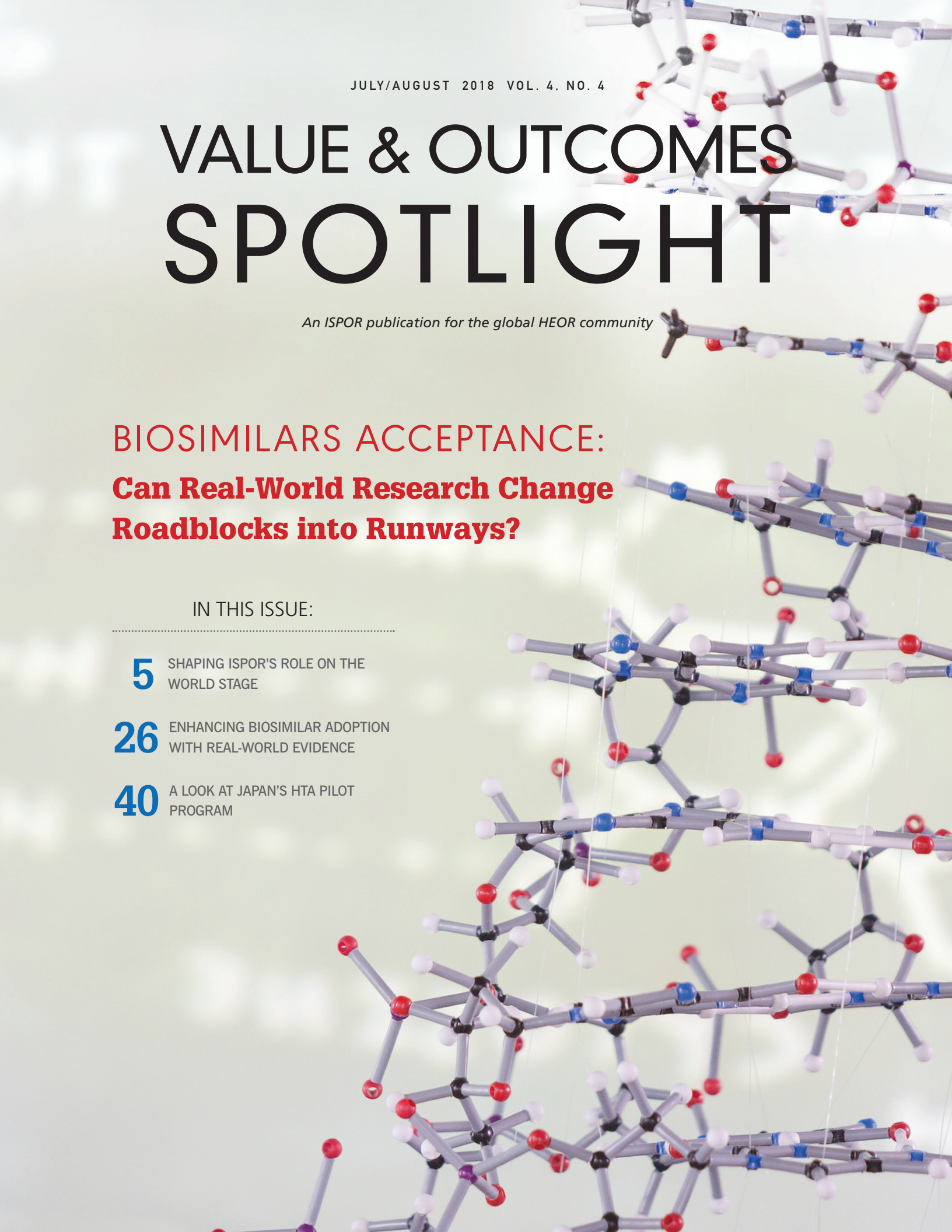
VALUE & OUTCOMES SPOTLIGHT

An ISPOR publication for the global HEOR community

BIOSIMILARS ACCEPTANCE:

Can Real-World Research Change Roadblocks into Runways?

IN THIS ISSUE:



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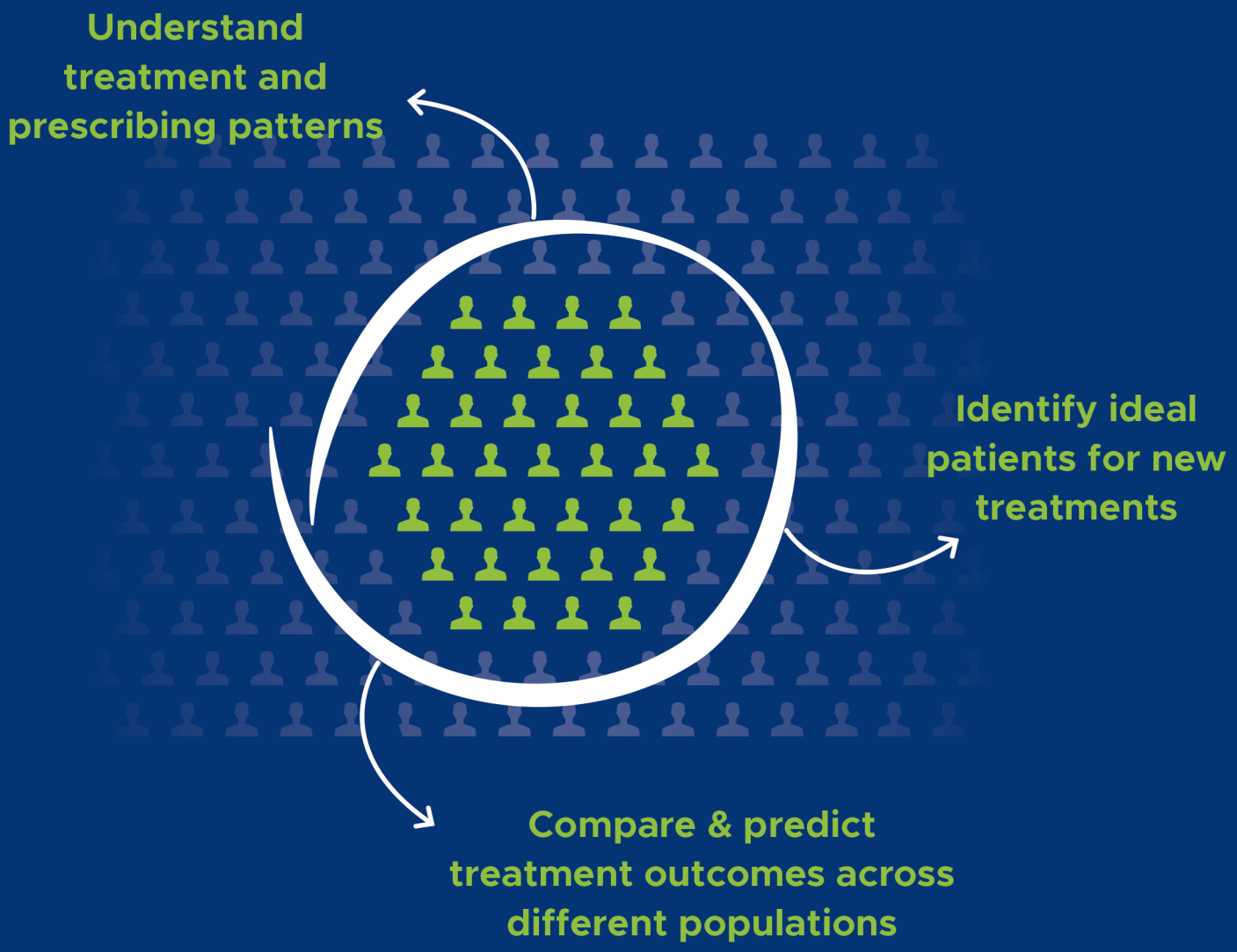

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VALUE & OUTCOMES
SPOTLIGHT

JULY/AUGUST 2018
VOL. 4, NO. 4

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ISPOR
Improving healthcare decisions

Editorial Staff
Stephen L. Priori
Director, Publications
spriori@ispor.org

Lyn Beamesderfer
Associate Director, Publications
and Communications
lbeamesderfer@ispor.org

Jennifer A. Brandt
Editorial Assistant
jbrandt@ispor.org

ISPOR Corporate Officers
Nancy S. Berg
Chief Executive Officer/
Executive Director
nberg@ispor.org

Richard J. Willke, PhD
Chief Science Officer
rwillke@ispor.org

Betsy Lane
Director and Chief Marketing
& Communications Officer
blane@ispor.org

ISPOR Headquarters
505 Lawrence Square Blvd, S
Lawrenceville, NJ 08648
Tel: 609-586-4981
Fax: 609-586-4982
info@ispor.org
www.ispor.org

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FROM THE EDITOR

Our theme for this issue of *Value & Outcomes Spotlight* is biosimilars. Global authorities (FDA, EMA, WHO) have aligned around a common definition of a biosimilar as a type of biologic developed specifically to have no clinically meaningful differences in terms of safety, efficacy, purity and biological activity in comparison with another biologic, commonly referred to as the "reference" or "originator" biologic.

It is tempting to think of biosimilars by way of analogy to generic drugs. One could imagine a tricky fill-in-the-blank question on a college entrance exam, "Generics are to branded drugs as _____ are to biologics." Perhaps a few high achievers would choose "biosimilars," but the correct answer would really be "none of the above," as biosimilars differ from biologics in so many ways, from development through regulatory approval to production and ultimately to marketplace entry. In all these respects a biosimilar's journey bears little resemblance to that of a small-molecule generic drug. Indeed, about the only thing biosimilars have in common with generics is a relatively lower price.

Biosimilars present a variety of challenges and opportunities for those of us in the ISPOR community. For instance, while originator biologics must follow the standard regulatory path towards gaining approval in various indications, painstakingly conducting trials in each, a key short-cut in the regulatory approval process for biosimilars is known as "extrapolation," which enables the developer of a biosimilar to gain approval conducting clinical research in just one indication but then having the product label include all of the indications of the originator biologic. The resulting data gaps present a challenge to economic modelers (no data to estimate model parameters) and an opportunity to practitioners of real-world research (need to conduct studies to fill these gaps).

Our feature article presents the current state of affairs on biosimilars and seeks to identify reasons why extrapolation and other issues are impeding market uptake. It appears that physicians, payers and patients alike are not so eager to climb on board the biosimilars bandwagon. Understanding the reasons why is key to unlocking the cost-saving potential of biosimilars. The good news is that HEOR and RWE can play a role in that, as elaborated upon in a second article on the topic and illustrated by means of a hospital case study in a third.

In addition to the biosimilars themed content, we include a variety of material of relevance to our Society. Our ISPOR Central section features the incoming presidential address from Federico Augustovski, who deserves heartfelt *felicidades* for being ISPOR's first president from the Latin American region. Upcoming conferences are highlighted as well, including the ISPOR Asia Pacific 2018 Conference in Tokyo. For those of you thinking of traveling to Japan for the meeting, we include an article summarizing the current state of that country's health technology assessment pilot program.

See you in Tokyo!

David Thompson, PhD
Editor-in-Chief,
Value & Outcomes Spotlight

ISPOR SPEAKS

Shaping ISPOR's Role on the World Stage

Federico Augustovski, MD, MSc, PhD, ISPOR President (2018-2019)

Although this photo is a current picture of me, my life with ISPOR has been quite long. Not as long as the "founding fathers and mothers," but rather long anyway. The smaller snapshot below shows a thirty something version of myself at the first Latin America ISPOR meeting in Colombia more than 10 years ago now.

Much has happened in these 10 long years—both for ISPOR as a whole and for me individually. I am very pleased to be serving as the 24th president of ISPOR. I recognize that I am here because of you. Sure, I had something to do about it, no doubt, but I´m here mainly because of you, the ISPOR community. I would like to thank all of you for the trust and the confidence you have placed in me.

My being here is the culmination of many things, some of them personal, but mostly as the result of a process ISPOR has been immersed in during the past several years. I am more inclined to view my involvement with ISPOR as a long journey—one that involves many encounters with people and institutions, rather than a single point in time. My ISPOR journey includes thousands of images—more like a movie, not a single snapshot. But when I look at the photos on this page, I cannot help but think about the significance of this moment in ISPOR's history. This one snapshot represents an important change in ISPOR's own journey. Not only does the snapshot depict ISPOR's first elected president from a "non-central" country or region, it also represents ISPOR's fulfilment of its longstanding commitment to diversity and inclusiveness. Paraphrasing the famous astronaut Neil Armstrong, I could say that this small step of electing a "non-central" president reflects a much bigger step for ISPOR in having a "built-in" global view—one that is less centered in the United States or Western Europe and that aims to incorporate a wide range of values and people.

THE ROAD AHEAD

I am really looking forward to serving as your president for the 2018-2019 term. What do I hope we can achieve this year and in the near future? I can contribute to balance the map a bit and make regions like Latin America, Asia, and Africa gain more prominence by helping to better blend our current ISPOR with other regional cultures, values, and knowledge to make ISPOR a broader, more diverse, and more inclusive Society.

As I look forward to my upcoming term as your president, I have been reflecting on the role ISPOR plays for its members and have been thinking about the themes I would like to focus on during my term. It has struck me that ISPOR is a very **diverse**, **innovative**, and **influential** Society.

DIVERSITY

ISPOR promotes inclusiveness by increasing its importance and influence beyond the United States and Europe and by promoting the growth of chapters and regional consortia. Diversity is an engine for creativity, inspiration, and success.

The integration of different backgrounds, geographies, types of education, formative paths, experiences, and training will have a significant impact in thinking and acting in a better way. I also consider it very important to keep making an effort to attract groups that are currently underrepresented in some regions, such as healthcare professionals, government decision makers, payers, and patients. Our new governance mandates and welcomes the participation >

of all regions in major groups such as the Health Science and Policy Council, Global Engagement Council, and more. No other organization is doing as much to capture the voices of its members in strategic and project-based activities.

We are also exploring ways to involve more mid-career people in important projects. Our Society is not an exclusive "VIP members only" club. It's for anybody who wants to get involved…and I encourage each of you to do just that. We will also be introducing to the membership more information on guidelines for submitting ideas for task forces and special task forces in an effort to promote transparency and inclusiveness.

INNOVATION

Innovation is a complex process that requires dialogue, creativity, and articulation. Innovations usually come in small, incremental steps that pave the way forward and intensify their downstream impact. Here are just a few examples of how ISPOR is innovating and making an impact:

- ISPOR is leading discussions with many stakeholders at a time when decision making is most difficult.
- ISPOR good research practice reports (particularly the CHEERS report) are now required in new employee training and in decision making in industry and governments settings.
- ISPOR is organizing the first patient roundtables in Latin America and Asia—areas where the patient voice is not so well integrated.
- ISPOR is beginning to "speak" to the media and to thought leaders through innovative projects like the Top 10 HEOR Trends report.
- ISPOR's outreach to other societies and organizations shows sincere desire to work collaboratively, not competitively.

INFLUENCE

Never has health economics and outcomes research been so needed and so valuable to decision makers. The expertise within our membership is needed in all corners of the world. ISPOR has begun to build a communication machine that will take our knowledge and resources to other stakeholders, including non-scientific parties that would benefit from ISPOR's pool of talent and expertise.

SHOULDERS OF GIANTS

In summary, we are all part of a diverse, innovative, and influential organization. Having these characteristics at our core helps us amplify the meaningful differences we all make to improve healthcare decisions around the world.

I hope we enjoy the journey as we travel down this path together. Together we can build a space that stimulates growth, mainly in advancing the science of HEOR, but also in creating long-lasting relationships where compromise and trust can flourish.

> …I could say that this small step of electing a "non-central" president reflects a much bigger step for ISPOR in having a "built-in" global view… that aims to incorporate a whole range of values and people.

The metaphor of dwarfs standing on the shoulders of giants aptly applies to the field of science where "discovering truth by building on previous discoveries" embodies what we do. This concept has been traced to the 12th century, and is most recognized in the sentiment expressed by Sir Isaac Newton: "If I have seen further it is by standing on the shoulders of giants."

This is where I—we—stand now…on the shoulders of the giants who built ISPOR, an organization that is rapidly approaching a quarter of a century with continuous growth and success. In my land, we dance the tango and drink Malbec wine. Two traditions that relate to sharing and enjoying. I hope we can keep sharing and enjoying, even without the tango and Malbec, as we work to advance the science that informs healthcare decisions.

RESEARCH ROUNDUP

Section Editors: **Gabriela Tannus Branco de Araujo, MSc** and **Marcelo Fonseca, MD, MSc**

Editor's Note: The following texts are simplified summaries of the published articles. They do not contain an opinion or an in-depth analysis on the results obtained by the authors. The selection of these works was made based on theme relevance, not a product of a literature review or of a methodological quality selection.

Biosimilars have been a great source of discussion, not only in terms of their interchangeability and quality, but also in relation to how best to assess their economic impact, going beyond merely comparing prices. We have selected two articles that discuss these and other aspects.

Global Acceptance of Biosimilars: Importance of Regulatory Consistency, Education, and Trust

Cazap E, Jacobs I, McBride A, Popovian R, Sikara K.
Oncologist. 2018. [Epub ahead of print May 16]. doi:10.1634/theoncologist.2017-0671.

The overall expectation with biosimilars is that they promote lower treatment costs while providing the same efficacy and safety effects, and consequently allow for a larger number of patients to be treated.

This review article demonstrates the evolution of the global scenario for biosimilars and identifies inconsistencies among regulatory requirements in different regions of the world.

Ongoing efforts to improve regulatory alignment were also analyzed, highlighting the importance of education as a crucial factor in generating trust and acceptance of biosimilars worldwide.

Biosimilars are a matter of interest in all countries, regardless of whether they are rich or developing nations, since there is an expectation of reducing costs and increasing access to treatment. The article may serve as a basis for understanding the regulatory implications that subsequently impacted HEOR issues around the world, as simply comparing prices is already a conduct long discarded in our field.

Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes

Cohen HP, Blauvelt A, Rifkin RM, Danese S, Gokhale SB, Woollett G.
Drugs. 2018;78(4):463–478. doi: 10.1007/s40265-018-0881-y.

Another major discussion related to biosimilars evaluation is regarding the use of health resources for their adoption or replacement of the original product.

To provide an answer regarding the issues of clinical similarity between biological products and their biosimilars, the authors conducted a systematic review of the literature where a total of 90 studies involving 14,225 patients were evaluated.

The authors state that although the use of each drug should be assessed individually, the risk of safety concerns related to immunogenicity or reduced efficacy of biosimilars use remains unchanged after switching from a reference biological drug to a biosimilar drug.

Understanding these factors is of great importance to HEOR professionals as the evaluation of biosimilars must overcome interchangeability barriers. Therefore, real-world data should be collected so that we can truly assess the economic impact that biosimilars will have on a health system.

HEOR NEWS

A diverse collection of relevant news briefs from the global HEOR (health economics and outcomes research) community.

1 Does Value-Based Pay Need to Slow Down? (Managed Healthcare Executive)

The transition to value-based care is chugging ahead, but many providers are struggling to take on the risk required for these models to succeed. That's according to Andrea Gelzer, MD, senior vice president and corporate chief medical officer for AmeriHealth Caritas, a managed care plan.

http://managedhealthcareexecutive.com/ahip/does-value-based-pay-need-slow-down

2 Should Pharmacists Be Allowed to Write Prescriptions? (Wiley)

Prescribing of medications has traditionally been restricted to physicians, but there is growing support to allow pharmacists to do so as well. A *British Journal of Clinical Pharmacology* review of a large number of studies in many countries reveals that diverse groups of stakeholders hold positive views and experiences around pharmacist prescribing.

http://newsroom.wiley.com/press-release/should-pharmacists-be-allowed-write-prescriptions

3 Changing Our Approach to Treatment Decision Making—An Interview with Amy Berman (Pharmaphorum)

Amy Berman is a senior program officer with The John A. Hartford Foundation, a private philanthropy dedicated to improving the care of older adults, as well as an author, blogger, and patient advocate living with stage IV breast cancer. She is a member of CancerCare's Patient Values Initiatives advisory board, helping to make sure that patients' values and priorities are incorporated into treatment decision making. Here, Amy reveals why she chose palliative care over curative treatments and discusses the challenges to integrating patient preferences into cancer treatment planning.

https://pharmaphorum.com/views-and-analysis/changing-approach-treatment-decision-making

4 US FDA's Patient Input Guidance Opens Door Wider to Social Media Data Collection (The Pink Sheet)

Following stakeholder criticism of an earlier discussion paper, draft guidance does not automatically foreclose use of social media data as the primary source of qualitative research; however, agency says entities submitting such data for regulatory review must ensure rigor in methodology and data integrity.

https://pink.pharmaintelligence.informa.com/PS123324/US-FDAs-Patient-Input-Guidance-Opens-Door-Wider-To-Social-Media-Data-Collection

5 Why the Medical Research Grant System Could Be Costing Us Great Ideas (The New York Times)

The medical research grant system in the United States, run through the National Institutes of Health (NIH), is intended to fund work that spurs innovation and fosters research careers. In many ways, it may be failing. It has been getting harder for researchers to obtain grant support. A study published in 2015 in *JAMA* showed that from 2004 to 2012, research funding in the United States increased only 0.8% year to year. It hasn't kept up with the rate of inflation; officials say the NIH has lost about 23% of its purchasing power in a recent 12-year span.

https://www.nytimes.com/2018/06/18/upshot/why-the-medical-research-grant-system-could-be-costing-us-great-ideas.html

6 Patients with a Deductible Have Seen Their Out-of-Pocket Costs for Brand Medicines Increase 50% Since 2014 (PhRMA)

Spending on medicines is growing at the slowest rate in years, but according to a new IQVIA Institute for Human Data Science article, at the pharmacy, commercially insured patients with a deductible have seen their out-of-pocket costs for brand medicines increase 50% since 2014. The data also show 55% of patients' out-of-pocket spending on brand medicines in 2017 was for prescriptions filled in the deductible or with coinsurance rather than with a fixed copay. This share has increased 20% since 2013 as insurers are increasingly shifting more and more of the costs of medicines to patients.

https://catalyst.phrma.org/patients-with-a-deductible-have-their-seen-out-of-pocket-costs-for-brand-medicines-increase-50-percent-since-2014

HEOR NEWS

7 New KFF Resource Tracks Proposed 2019 Marketplace Premiums by State (Kaiser Family Foundation)

The Kaiser Family Foundation recently launched a tracker to monitor preliminary 2019 premiums in the Affordable Care Act's marketplaces as insurers file rate information with state regulators. Beginning with data from 8 states (Maine, Maryland, New York, Oregon, Rhode Island, Vermont, Virginia and Washington) plus the District of Columbia, the tracker shows preliminary premium information in 9 major cities for the lowest-cost bronze plan and "benchmark" silver plan, which is used to determine the size of the premium tax credits available to low- and moderate-income enrollees.

https://www.kff.org/private-insurance/press-release/tracks-proposed-2019-marketplace-premiums-by-state/

8 Profits in the 2018 Fortune 500: Manufacturers vs Wholesalers, PBMs, and Pharmacies (Drug Channels)

This Fortune 500 list is a popular post every year because it helps follow the dollar and understand how drug channel intermediaries make money. This analysis also provides crucial background for understanding the Trump administration's drug pricing blueprint.

https://www.drugchannels.net/2018/06/profits-in-2018-fortune-500.html

9 The Age of Longevity: Is Our Healthcare System Ready for Our Aging Society? (Cardinal Health)

At the University of Michigan's Paul F. Glenn Center for Aging Research, Richard A. Miller, MD, PhD, a professor of pathology and one of the nation's leading experts on the biological aging process, is trying to turn back the clock on the human body. Using mice, Miller and his team are testing the effects of different drugs for their ability to delay aging, and they're accomplishing some remarkable results. It sounds like science fiction, but Dr Miller is adamant that it really could happen. Unfortunately, though, he added, the resources for aging research just aren't there. And that's too bad, because the United States is quickly embarking on the age of longevity—where people are living longer, but not necessarily healthier, lives—and our current health system may not be equipped to handle it.

https://www.cardinalhealth.com/en/essential-insights/is-our-healthcare-system-ready-for-our-aging-society.html

10 Medicare Eyes Hospital Readmissions from Nursing Homes (MedPage Today)

With hospitals pushing patients out the door earlier, nursing homes are deluged with increasingly frail patients. But many homes, with their sometimes-skeletal medical staffing, often fail to handle post-hospital complications—or create new problems by not heeding or receiving accurate hospital and physician instructions.

https://www.medpagetoday.com/geriatrics/generalgeriatrics/73578?xid=nl_mpt_investigative2018-06-19&eun=g534639d0r&utm_source=Sailthru&utm_medium=email&utm_campaign=InvestigateMD_061918&utm_term=Pop%20Medicine

11 Who Cares About a Label? The Effect of Pediatric Labeling Changes on Prescription Drug Utilization (UCLA)

Off-label drug use is common, particularly in pediatric populations. In response, recent legislation requires and/or provides financial incentives for drug manufacturers to perform pediatric clinical trials. This examines the impact of subsequent changes to drug labeling on pediatric drug utilization.

https://www.anderson.ucla.edu/Documents/areas/fac/policy/OdySchmitt_PediatricLabeling.pdf

12 Participation in OCM May Transform Care for Certain Cancer Types More Quickly Than Others (AJMC)

Approximately 21% of Medicare patients with cancer are now receiving care from a physician participating in the Oncology Care Model (OCM), but with representation of cancer types varying, trends of participation in OCM could actually skew the transformation of cancer treatment more heavily for some cancers, according to Avalere Health. A new report found that breast and lung cancers were the more common types of cancers with more than 25% of patients with breast and lung cancers treated by a doctor participating in the OCM.

https://www.ajmc.com/newsroom/participation-in-ocm-may-transform-care-for-certain-cancer-types-more-quickly-than-others

CONFERENCES & EDUCATION

ISPOR Asia Pacific 2018

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Plenary sessions:

Transforming Healthcare and Leveraging Digital Health for Better Health in Asia Pacific, explores the current challenges and possibilities in digital health in the region, with important insight about how to grasp benefits and potential from those furthest in their digital journey.
Moderator: **Erwin Loh, MBBS, MBA, MHSM, PhD**, Monash Health, Melbourne, Australia; *Speakers:* **Gabe Rijpma**, Microsoft Asia, Auckland, New Zealand; **Polawat Witoolkollachit, MD**, Ministry of Public Health, Bangkok, Thailand; **Jilan Liu, MD, MHA**, Joint Commission International, and Healthcare Information and Management Systems Society, Seattle, USA; **Huei-Xin Lou, PharmD, MSc**, Integrated Health Information Systems Pte Ltd, and Ministry of Health, Singapore.

Real-World Evidence in Asia Pacific: Are We Ready? Is It Helpful for Decision Makers? discusses the reality of real-world evidence (RWE) and its potential value, examines readiness of RWE in healthcare decision making. This session explores how we should approach RWE to get the most out of it. Speakers from various sectors will share their perspectives and experiences.
Moderator: **Bart Barefoot**, GlaxoSmithKline, London, UK; *Speakers:* **K. Arnold Chan, MD, ScD**, National Taiwan University Hospital and Drug Safety Committee of FDA, Taipei, Taiwan; **Xin Sun, PhD**, West China Hospital, Sichuan University, Chengdu, China; **Manabu Akazawa, PhD, MPH**, Meiji Pharmaceutical University, Tokyo, Japan.

Risk Sharing Agreements: Country Experiences, Challenges, and Lessons Learned, will discuss the use of risk sharing agreements (RSAs) to manage costs, mitigate risk, and improve patient access to innovative therapies. Key issues and practical challenges in implementing RSAs will be addressed.
Moderator: **Joerg Mahlich**, Janssen Pharmaceutical, and Janssen Japan KK, Neuss, Germany; *Speakers:* **Elizabeth de Somer**, Medicines Australia, Canberra, Australia; **Youngjin Song**, Ministry of Health and Welfare, Seoul, South Korea; **Gergana Zlateva, PhD**, Pfizer Inc, New York, USA.

18 Short Courses including these 5 NEW Sessions:

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– Medical Devices in Asia Pacific: Regulatory and Reimbursement Issues
– Budget Impact Analysis II: Applications and Design Issues
– Applied Modeling
– Introduction to Big Data Analysis: Graph Analytics

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Ola Ghaleb Al Ahdab, PhD
Fatima Albreiki, PhD, EMHCA, BSc Pharm
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– Pricing and Reimbursement: Issues and Challenges
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Value in Health

Call for Papers

Back to the Future:
A 20th anniversary issue of *Value in Health*

To mark *Value in Health's* 20th anniversary, the Editors are commissioning articles for a "Back to the Future" theme that features topics that have been widely discussed in the journal over the past 20 years, but for which there is an exciting future agenda.

The themed section is tentatively scheduled to appear in the January 2019 issue of *Value in Health*. Submissions received before **August 1, 2018** have the best chance for inclusion.

The Editors are soliciting proposals for papers on any topic, no matter how unconventional. This is the time to be creative.

Potential topics might include, but not restricted to:

- How has the definition of value in healthcare changed over the past two decades?
- How have regulatory agencies' views evolved regarding their role in determining value in healthcare?
- If QALYs have inadequacies, what would an alternative measure of benefit look like?
- The exponential growth in cost-effectiveness analyses suggests that their importance and impact has matured, but is there empirical evidence for that?
- If Markov models are the norm, how would we decide that we need alternative modeling approaches?
- Has the increased complexity of health economic models advanced the field by improving scientific validity or further confused decision makers?

Authors should submit manuscripts through our web-based tracking system at https://mc.manuscriptcentral.com/valueinhealth and indicate in the cover letter that it is part of the "Back to the Future" themed section.

For more information about *Value in Health* visit **www.ispor.org**.

***Value in Health* Editorial Office**
505 Lawrence Square Blvd South, Lawrenceville, NJ 08648

ISPOR
Improving healthcare decisions

FROM THE JOURNALS

The following Editors' Choice articles appear in the July and August 2018 issues of *Value in Health.*

For more information, visit: www.ispor.org/valuehealth_index.asp.

July 2018

BRIEF REPORT

Use and Misuse of Cost-Effectiveness Analysis Thresholds in Low- and Middle-Income Countries: Trends in Cost per Disability Adjusted Life-Years Studies

Ashley Leech, David Kim, Joshua Cohen, Peter Neumann

Previous literature has addressed pros and cons of using generic economic thresholds to determine the cost-effectiveness of an intervention, while other studies have pointed to alternative approaches to valuing care. In this brief report, the authors examine the evolution of thresholds in the cost-effectiveness literature for low and middle-income countries and analyze whether these studies appropriately justified the use of these values.

ECONOMIC EVALUATION

Cost-Effectiveness Analysis in Telehealth: A Comparison between Home Telemonitoring, Nurse Telephone Support, and Usual Care in Chronic Heart Failure Management

Andrija S. Grustam, Johan L. Severens, Daniele De Massari, Nasuh Buyukkaramikli, Ron Koymans, Hubertus J.M. Vrijhoef

The aim of this study is to provide insights into the cost-effectiveness of a telehealth (ie, telemonitoring) system in The Netherlands from a third-party payer's perspective. The authors assessed whether home telemonitoring or nurse telephone support were cost-effective strategies in the management of congestive heart failure, compared with usual care. They also explored whether there is a subgroup of congestive heart failure patients that can benefit the most from telemonitoring.

PREFERENCE-BASED ASSESSMENT

Uncertainty and the Under-Valuation of Services for Severe Health States in Cost Utility Analyses

Jeff Ralph Richardson, Angelo Iezzi, Aimee Maxwell

A number of psychological factors that affect measurement under uncertainty do not affect utility as currently measured. The aim of this study was to test the 'uncertainty aversion hypothesis' by generating a scoring algorithm weighted on the preferences of consumers for assessing the quality of care in nursing homes.

August 2018

COMPARATIVE-EFFECTIVENESS RESEARCH/HTA

Surveying the Cost-Effectiveness of the Twenty Procedures With the Largest Public Health Services Waiting Lists in Ireland: Implications for Ireland's Cost-Effectiveness Threshold

Tse Chiang Chen, Dane Wanniarachige, Síofra Murphy, Katie Lockhart, James O'Mahony

The authors survey the cost-effectiveness of procedures with the largest waiting lists in the Irish public health system in order to inform a reconsideration of Ireland's current cost-effectiveness threshold of €45,000/quality-adjusted life-year.

ECONOMIC EVALUATION

Productivity Benefits of Medical Care: Evidence from US-Based Randomized Clinical Trials

Alice Chen, Dana Goldman

This paper examines the relationship between new drug treatments and gains in labor productivity across conditions in the United States and evaluates which randomized clinical trials collect productivity data.

HEALTH POLICY ANALYSIS

Comparing the ICERs in Medicine Reimbursement Submissions to NICE and PBAC: Does the Presence of an Explicit Threshold Affect the ICER Proposed?

Shuhong Wang, Debra Gum, Tracy Merlin

The authors compared the initial incremental cost-effectiveness ratios (ICERs) presented by manufacturers in matched submissions to each decision-making body, with the aim of exploring the impact of an explicit threshold on these ICERs.

METHODOLOGY

Sharing and the Provision of 'Cost Ineffective' Life-Extending Services to Less Severely Ill Patients

Jeff Richardson, Angelo Iezzi, Aimee Maxwell

This paper examines whether this preference for sharing persists for less severe conditions when both cost-effectiveness and illness severity would indicate that resources should be allocated to other services.

PATIENT-REPORTED OUTCOMES

Patient-Reported Outcome Measures in the FDA Pilot Compendium: Meeting Today's Standards for Patient Engagement in Development?

Elisabeth Oehrlein, Eleanor Perfetto, Thelma Love, Yujin Chung, Parima Ghafoori

In 2016, the US FDA released a Pilot Clinical Outcome Assessment Compendium intended to foster patient-focused drug development. In this study, the authors find that most of the patient-reported outcomes measures in the sample examined violate a fundamental premise to engage patients in the development process.

PREFERENCE-BASED ASSESSMENTS

Advocating a Paradigm Shift in Health-State Valuations: The Estimation of Time-Preference Corrected QALY Tariffs

Marcel Jonker, Bas Donkers, Esther de Bekker-Grob, Elly Stolk

This paper introduces a general method of accommodating for non-linear time preferences in discrete choice experiment duration studies and to evaluate its impact on estimated QALY tariffs.

FROM THE JOURNALS

The following Editors' Choice articles appeared in the May 2018 issue of *Value in Health Regional Issues.*

Appropriate use of health economics and outcomes research (HEOR) can provide detailed insight and profound information for healthcare decision makers. Healthcare systems in Asia Pacific countries are facing many challenging tasks and implementing reform policies. The research published in *Value in Health Regional Issues* can help educate readers and healthcare stakeholders about how to use HEOR for emerging themes in the Asia Pacific region. For more information about the journal and to read the current issue, visit: https://www.ispor.org/publications/VIHRI/index.asp

THEMED SECTION: DRUG POLICIES IN ASIA

Recent Pricing Negotiations on Innovative Medicines in China: Experiences, Trends, and Implications

Hong Li, Gordon Liu, Jing Wu, Jiu-Hong Wu, Chao-Hui Dong, Shan-Lian Hu

New Drug Reimbursement and Pricing Policy in Taiwan

Gau-Tzu Chen, Shu-Chen Chang, Chee-Jen Chang

Health Technology Assessment and Its Use in Drug Policies in China

Xuemei Zhen, Xueshan Sun, Hengjin Dong

ECONOMIC EVALUATION

Modeling Possible Inclusion of Pneumococcal Conjugate Vaccine into the National Immunization Program for Infants in India

Canna Ghia, Matt Wasserman, Mark Fletcher; Ray Farkouh, Gautam Rambhad

Using a well-established pneumococcal disease impact model parameterized with local data to the extent possible, the authors calculated the potential impact of introducing an infant pneumococcal conjugate vaccine program in India.

PATIENT-REPORTED OUTCOMES

Health-Related Quality of Life of Patients With Human Papilloma Virus-Related Cancers in Indonesia

Antoinette D. van Asselt, Arrum Dusafitri, Didik Setiawan, Githa F. Galistiani, Maarten J. Postma

In comparison to existing reference utility index for healthy population, health-related quality of life of patients with human papilloma virus-related cancers was found to be reduced to a certain extent in this study in Indonesia.

BOARD OF DIRECTORS

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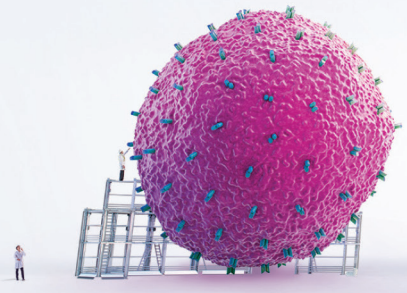

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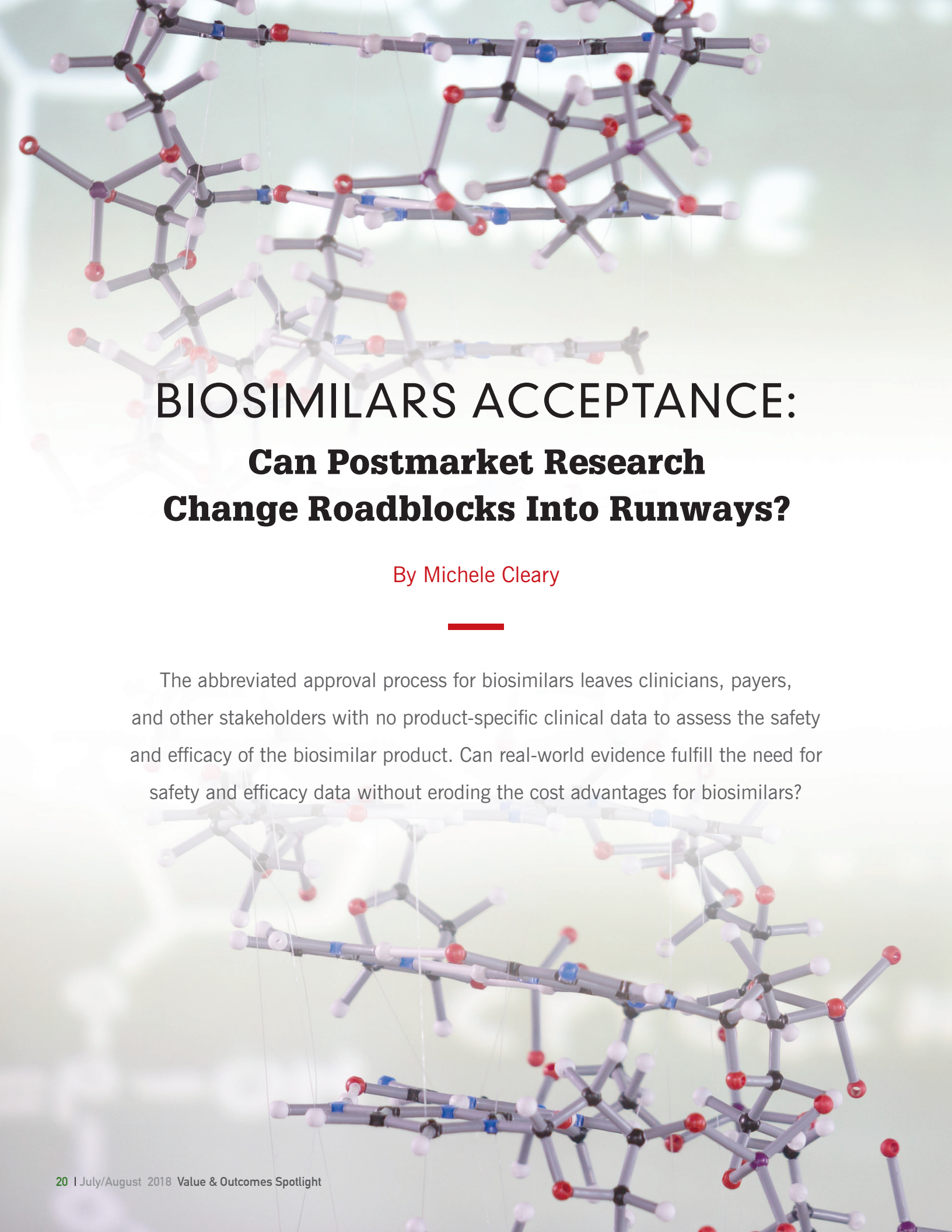

BIOSIMILARS ACCEPTANCE:

Can Postmarket Research Change Roadblocks Into Runways?

By Michele Cleary

The abbreviated approval process for biosimilars leaves clinicians, payers, and other stakeholders with no product-specific clinical data to assess the safety and efficacy of the biosimilar product. Can real-world evidence fulfill the need for safety and efficacy data without eroding the cost advantages for biosimilars?

Biologics have revolutionized healthcare, bringing hope and relief to millions suffering from conditions ranging from cancer and multiple sclerosis to psoriasis and rheumatoid arthritis.[1] Yet these critically important advancements have come at a tremendous cost. Despite these products being used by only 1% to 2% of the US population, biologics account for 38% of the nation's prescription drug expenditures, accounting for 70% of the growth in drug spending between 2010 and 2015.[2,3] Biologics are consuming healthcare budgets at an unsustainable rate, forcing payers to make difficult choices regarding access and coverage. The complex development and manufacturing processes for biologics, coupled with small markets from which to recoup development costs, not only contribute to the hefty price tag but also nearly extinguish competition.[4]

ENERGIZING MARKETS WITH BIOSIMILARS

Biosimilars have been heralded for bringing much-needed competitive pressure to the biologic market. These products are deemed to be "highly similar" to specific reference biologic products with *no clinically meaningful* differences with regard to safety, purity, or potency.[5,6] By providing comparable therapeutic benefit, biosimilars have the potential to lower prices within the biologic market at a time when drug prices are a national crisis.

Global regulatory bodies have recognized the need to encourage biosimilar development and to hasten their entry into the market. In the United States, the 2010 Biologics Price Competition and Innovation (BPCI) Act created the 351(k) approval pathway for biosimilars, an abbreviated pathway to approval by the US Food and Drug Administration (FDA). Under BPCI, sponsors need not re-establish the safety and efficacy of their biosimilar candidate, thus eliminating the need for extensive phase I-III trials.[7] Instead, sponsors can demonstrate their product's biosimilarity to its biologic reference product and thereby rely on the FDA's earlier determination of the reference's safety and efficacy. Once biosimilarity is established for one indication, the biosimilar can be approved for other indications through extrapolation. In other words, effectiveness is extrapolated to other indications without clinical data. Despite much debate about its validity, extrapolation provides a critical cost-savings mechanism to enhance market entry by biosimilars.

THE ANEMIC ADOPTION OF BIOSIMILARS

Thus far, biosimilars have failed to affect the biologics market as previously hoped. While the FDA has approved 11 biosimilars, only 3 are currently marketed in the United States.[8] And these 3 have demonstrated only modest impact on the prices of reference biologics (price drops of 15%-35%).[9/12] While contracting and coverage issues have created market impediments from a payer perspective, survey data have shown that clinicians remain cautious about biosimilars, concerned about the lack of further evidence of the products' safety and efficacy.[13]. For stakeholders committed to evidence-based treatment decisions, extrapolation to an indication may be fueling prescriber skepticism and perhaps has slowed the adoption of biosimilars.

Recent surveys have revealed that many clinicians are uneasy with the FDA's abbreviated approval process for biosimilars and with extrapolating to an indication without clinical data supporting a product's safety and efficacy.[13-15] A 2015 Quantia physician survey found that despite 94% of respondents viewing biosimilars as providing value to the healthcare system, less than 20% of prescribing specialists reported being "very likely" to prescribe biosimilars to eligible patients.[16,17] This reluctance appears to be due to residual concerns over the safety and efficacy of biosimilars, as many respondents voiced concerns about their safety and efficacy and shared that they were eager to review products' clinical data. The Biosimilars Forum found specialty physicians reported a similar desire for additional safety and efficacy information when considering a biosimilar, with 13% of respondents stating that they could not fully trust the FDA's assessments and that they would seek additional information before prescribing a biosimilar.[13] This survey found only 12% of respondents reported feeling completely comfortable with the concept of extrapolation, while more than one-third felt that an abbreviated approval process translates to a greater safety risk. These safety concerns were most prevalent among dermatologists and rheumatologists at 43% and 48%, respectively.[13]

Surveys also identified confusion among prescribers regarding when to introduce a biosimilar. A 2016 survey of specialty physicians found that these clinicians were more comfortable limiting biosimilars to their treatment-naïve patients rather than switching stable patients from a biologic to a biosimilar.[18] A reluctance to switch stable patients to a biosimilar was also identified in a separate 2016 study; only 1 of 8 rheumatologists surveyed said that they would switch a stable patient from a reference product to a biosimilar.[17] However, switching may be influenced by factors independent of treatment efficacy.

Physicians who choose to use biosimilars strictly in their treatment-naïve patients may have an easier time gaining patient acceptance than with patients who are stable on a reference biologic (payer step-care policies may also preclude this approach). Prescribers considering switching patients from a reference biologic to a biosimilar may require additional patient support to answer questions regarding why the change in treatment. Alternatively, a specific indication may influence the decision to switch when physicians treating more dire conditions (eg, cancer) may be less comfortable using a biosimilar with extrapolated indications.

Physicians have asserted that clinical trial data could improve their understanding of biosimilars and help them integrate biosimilars into their practices.[17] These survey data support further physician education initiatives that outline the differences between biosimilars and reference biologics, as well as the role extrapolation plays between the two. Physicians desire additional safety and efficacy data for biosimilars, as well as further research into treatment switching patterns. However, additional data on safety and efficacy could also help payers make informed decisions about coverage. Some hospitals and health systems may reserve biosimilars only for treatment-naïve patients or may require patients to fail first on the reference biologic—which makes it very unlikely that a biosimilar would be used.[19] In these cases, additional data on safety and efficacy, especially research into how switching impacts patient outcomes, may persuade payers to cover biosimilars on par with their reference biologics. >

COULD REAL-WORLD EVIDENCE SPUR BIOSIMILAR ACCEPTANCE?

The abbreviated approval approach provides biosimilars with an important cost advantage by approving the products for indications through extrapolation rather than through extensive clinical trial data. Yet many stakeholders express unease with the lack of safety and efficacy data specific to the biosimilar product. While manufacturers could develop a research agenda of rigorous trials that could fill this data gap caused by extrapolation, doing so would also severely reduce or eliminate the cost advantage biosimilars bring to the market, eliminating whatever competitive pressure biosimilars impose on biologic prices. However, real-world evidence (RWE) may fulfill this need for further safety and efficacy data without eroding biosimilars' cost advantage. RWE could also provide important information on other lingering prescriber questions regarding optimal treatment outcomes for different subpopulations or whether switching leads to diminished efficacy. Luckily, multiple data resources exist to collect and analyze biosimilar RWE.

> For stakeholders committed to evidence-based treatment decisions, extrapolation to an indication may be fueling prescriber skepticism and perhaps has slowed the adoption of biosimilars.

The Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) is a multistakeholder, nonprofit, scientific public service initiative that helps provide cost-effective postmarketing data. BBCIC utilizes Sentinel administrative data to monitor the safety and effectiveness of biosimilars and reference biologics, developing best practices for researching outcomes and methodologies for specific indications.[20] The group is currently considering expanding its data capabilities by including electronic health records, laboratory data, and patient- and clinician-reported outcomes in order to expand its analytic capabilities. Their input could be critically important to fill the information payers and providers need to inform their evidence-based decisions. Manufacturers could further disseminate BBCIC findings to plans and providers to reinforce/establish comfort with biosimilars' extrapolated results.

While BBCIC's Sentinel data analyses may be ideal for analyzing safety and efficacy of older biosimilars, the data lag associated with administrative claims data makes the Sentinel data inadequate for newly approved biosimilars (and those that have not hit the market). For newer biosimilars, international data would prove invaluable. To date, the United States has approved 11 biosimilars (only 3 of which have reached the market), while Europe has approved more than 40 biosimilars, with millions more years of patient exposure, since 2006.[21]

International data sources could provide a rich resource from which to analyze the safety and efficacy of biosimilar products in different patient subpopulations and for different indications. They can also be a valuable resource to study outcomes in treatment-naïve patients versus those switched from a biologic. In addition, while there may also be interesting observations in terms of practice patterns and switching, other confounding factors could limit direct comparisons; differences in health systems may affect treatment choices differently. Yet the years of experience with these products could answer many stakeholder concerns about biosimilars both currently on the market in the United States and those soon to come onto the market.

To aid in these analytic efforts, ISPOR is starting a special interest group on biosimilars. ISPOR's biosimilar group may help develop postmarketing surveillance guidelines for biosimilars so that there will be sufficient information to address stakeholder concerns regarding biosimilar safety and efficacy without eroding biosimilars' cost advantages. This group may address how international data may be used to collect RWE on newer biosimilars; how to best study switching outcomes; and what are ideal reference groups for switching studies. This group will also incorporate a broad mix of stakeholders to not only provide the most accurate and relevant information but also to disseminate findings to ensure maximum and timely benefit.

EFFECTIVE DISSEMINATION OF FINDINGS

Because many clinicians have lingering questions about the safety and efficacy of biosimilars, these clinicians are eager to learn more about the treatment outcomes associated with specific biosimilars before prescribing these products to their patients. Prior survey data confirm that both clinicians and patients become far more comfortable with biosimilars when they learn more about the products' safety and efficacy, and they are more likely to prescribe these products when equipped with these data.[18,22-24]

Disseminated data can also be incorporated into patient education materials to help counteract the barrage of direct-to-consumer advertising for reference biologics, while also mitigating patient nocebo effects, which has been demonstrated in clinical trials to negatively affect acceptance in patients switching from an originator product to a biosimilar.[25,26] Finally, payer stakeholders who determine formulary placement and reimbursement policies have significant control over how quickly biosimilars may be adopted into practice, and hence should be included in the first wave of data dissemination. Efficient dissemination of postmarketing data and analyses to all stakeholders will promote more rapid adoption of biosimilars into clinical practice. In addition, as biosimilars are more widely prescribed, the price-correcting competitive pressure from biosimilars will become more effective.

Since its launch of the Biosimilar Education and Outreach Campaign in October 2017, the FDA has taken a proactive role in educating healthcare practitioners, payers, and patients about biosimilars, their clinical benefits, and their potential value to patients. The Agency may be an effective partner in disseminating biosimilar research data. In addition to scientific journals and conferences, biosimilar data could also be shared with relevant specialty societies, as past surveys found that these societies were prescribing specialists' most trusted source of information on biosimilars.[27] Possible with input from BBCIC, the FDA, or the Biosimilars Forum, which provides evidence-based information

to inform and support public policies that encourage access and adoption of biosimilars, could also be employed.

Finally, while disseminating these postmarketing research findings, stakeholders may benefit from a review of the FDA's stance on the biosimilar approval process and extrapolated indications [7]:

> "The abbreviated licensure pathway is not a lower approval standard for biosimilar biologic products. Rather, the abbreviated pathway allows for reliance on the FDA's previous finding of safety and effectiveness for the reference product, promoting a potentially shorter, or abbreviated, and less costly development program.
>
> "Given the totality of the evidence approach and the scientific basis for extrapolation applied in the 351(k) licensure pathway, approval of a biologic product as biosimilar to a reference product means that patients and physicians can rely on the safety and effectiveness of the approved biosimilar product in the same way that they would for the reference product in each condition of use for which the biosimilar product is used."

BUILDING A MARKET FOR FUTURE BIOSIMILARS

Biosimilars have the potential to save our health system billions by injecting critical competitive pressure into the biologics market. Yet to influence prices in the market effectively, biosimilars must achieve sufficient market share. However acceptance of biosimilars has been slow due to persistent prescriber confusion and apprehension surrounding the safety and efficacy of the biosimilars.

Biosimilars can enter these markets thanks to extrapolated indications that require minimal clinical data. But this extrapolation process leaves payers, clinicians, and other stakeholders making evidence-based decisions with insufficient clinical data to fully support the use of biosimilars. Postmarketing analyses using either foreign or domestic data sources can provide the data necessary to quell any lingering doubts about safety and efficacy, while also informing best practices by indication and by patient type. These data will not only build stakeholder confidence in biosimilars, but they can also strengthen the biosimilar market sufficiently to ensure the entry of biosimilars long into the future.

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About the Author:

Michele Cleary is an HEOR researcher and scientific writer with more than 15 years of experience in the healthcare field.

Additional information:

For more information on ISPOR and biosimilars, contact sigs@ispor.org.

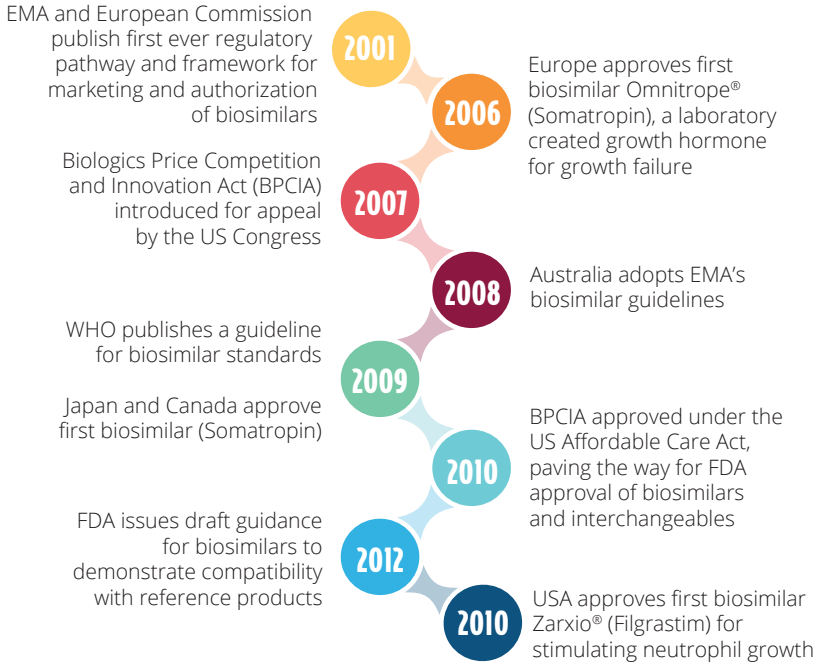
By the Numbers: Biosimilars

Section Editor: The ISPOR Student Network

DISTRIBUTION OF APPROVED BIOSIMILARS BY THERAPEUTIC AREA, FDA VS EMA

Therapeutic Area	FDA[1]	EMA[2]
Rheumatology	40%	27%
Oncology	20%	22%
Infectious diseases	10%	20%
Hematology	10%	12%
Endocrinology	0%	10%
Gynecology	0%	5%
Gastroenterology	20%	0%
Cardiology	0%	2%
Medical genetics	0%	2%

TIMELINE FOR BIOSIMILARS[1,2,3]



STAKEHOLDER PERSPECTIVES ON BIOSIMILARS

PHYSICIANS' PERSPECTIVE[4,5]

- 80% are ready to consider pharmacy-level substitution of biologics with biosimilars
- 33% of patients are not confident about biosimilars even when prescribed and explained by the treating physician
- 17% feel biosimilars will become the norm in the next 3 years

PATIENTS' PERSPECTIVE[6,7]

- 90% patients believe that they had the right to make an informed choice about their treatment and did not support automatic substitution of a biosimilar for a reference product.
- 75% were concerned about the extrapolation of indications for biosimilars

PAYER PERSPECTIVE[8]

- 88% believe that biosimilars will reduce specialty drug prices
- 80% consider biosimilars to be lower-cost branded options and not generics
- UK payers expect biosimilar market share to be 80% in next 5 years

Contributors: Gary O'Brien, University College Cork; Aakash Gandhi, University of Maryland; Jayesh Patel, West Virginia University; Simrun Grewal, University of Washington; Koen Degeling, University of Twente

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Enhancing Biosimilar Adoption With Real-World Evidence

Sarah Ronnebaum, Chris Atzinger, Pharmerit International, Bethesda, MD, USA

KEY POINTS

Biosimilars have the potential to improve access to effective therapies by lowering costs, but their demand is regulated by physicians.

Physicians express reservations regarding biosimilar safety, efficacy, and immunogenicity, and may require additional evidence to prescribe biosimilars.

Real-world evidence studies can address evidence gaps and convince all stakeholders, including physicians, about long-term biosimilar use in specific populations.

INTRODUCTION

Biologics comprise nucleic acids, proteins, and/or sugars within complex molecular structures and are derived from living organisms, as opposed to traditional small-molecular medicines.[1] Biosimilars are highly similar to existing biologics in biological, safety, efficacy, and purity characteristics.[1] Because of savings in research and discovery, clinical trials, and production, biosimilars can be offered at lower prices than originator biologics, creating the potential for cost savings while enabling consistent therapeutic access for patients.[2] Future biosimilar development and possible cost savings depend on the extent of biosimilar adoption.[3]

Biosimilar adoption is influenced by regulatory frameworks, economic incentives, clinical evidence, and patient preferences; these factors vary widely across markets.[4] Physician confidence in biosimilars has been recognized as an important factor in adoption across global markets.[4] The objective of this review is to summarize attitudes towards biosimilars among physicians and provide recommendations for enhancing biosimilar adoption using real-world evidence (RWE).

ATTITUDES TOWARDS BIOSIMILARS AMONG PHYSICIANS

While the approval of a biologic is based mainly on clinical studies demonstrating efficacy and safety, biosimilar approval is focused mostly on analytical studies that demonstrate high molecular similarity and equally low levels of impurities to the originator biologic.[2] A biosimilar may be approved for the same indications as the originator biologic without being tested directly in all indicated populations (referred to as extrapolation), provided that the biosimilar is equivalent to the originator biologic in at least 1 indication.[2] Studies demonstrating the safety of switching from the originator biologic to the biosimilar are not required for approval. Consequently, key concerns for physicians and patients about biosimilars include safety, efficacy (particularly in extrapolated indications), immunogenicity, and effects of switching to a new biosimilar, possibly due to perceptions of insufficient study follow-up time or clinical data collection.[5] Globally, some physicians believe the abbreviated approval process for biosimilars suggests reduced product safety, and many physicians are hesitant to switch patients from originator products to biosimilars without evidence from switching studies.[1,6]

> Physicians are the main gatekeepers in determining whether patients receive an originator biologic or biosimilar.

In addition to efficacy and safety concerns, biosimilar familiarity and acceptance vary across individual markets due to market maturity, prescribing policies, and other factors. Europe has the most mature biosimilar market, having developed the first regulatory framework for approving biosimilars in 2005.[5] Likewise, a higher proportion of European physicians report biosimilar familiarity and acceptance as compared to counterparts in the United States, Japan, and Latin America.[6-9] When examined closely, these survey results suggest incomplete acceptance among physicians globally and fundamental differences in acceptance across markets. Some differences may be related to different regulatory and economic incentives for providers across markets. European countries may enforce a minimum quota of certain biosimilars, encourage a certain minimum percentage of biosimilars be prescribed for treatment-naïve patients, or compel the physician to prescribe the most cost-effective product.[10, 11] There is no uniform, systematic incentive for biosimilar prescribing in the United States, where payers and pharmacy benefit managers play influential roles in pricing and availability, although biosimilar prescribing may be encouraged in some instances.[12]

Physicians also need evidence of biosimilar safety and efficacy to share with patients who may be reluctant to switch from a biologic to a biosimilar.[13] In addition, several professional medical societies explicitly state that the patient's awareness and consent are required for a physician to prescribe a biosimilar.[1]

THE ROLE OF SUBSTITUTION IN BIOSIMILAR DEMAND

Physicians are the main gatekeepers in determining whether patients receive an originator biologic or biosimilar. Unlike generic versions of small molecules, pharmacists cannot dispense a biosimilar in place of the originator biologic without the direct consent of the prescribing physician (referred to as substitution) in many markets.[14] In the United States, only the US Food and Drug Administration (FDA) can determine whether a biosimilar is interchangeable (referring to the highest degree of biosimilarity to the originator biologic as to allow pharmacist substitution) with its originator.[1] But as of May 2018, there are no FDA-designated interchangeable products,[15] and most states have passed legislation declaring that pharmacist substitution is contingent on the FDA's interchangeability approval.[16] Many professional medical societies throughout Europe, Canada, the United States, and Australia also oppose biosimilar substitution.[1]

EVIDENCE NEEDS AND CHANNELS FOR PHYSICIANS

Taken together, these survey results indicate that physicians act as a major regulator in biosimilar demand, but safety, efficacy, and immunogenicity concerns may hinder biosimilar adoption. Physicians throughout Europe, the United States, and Japan express a need for more high-quality information communicated in an ongoing manner on biosimilar safety, efficacy, comparability to the originator biologic, extrapolation, and cost.[6,9,10] But even in mature markets such as Europe, few countries provide biosimilar education specifically targeting physicians.[11]

Manufacturers can enhance biosimilar adoption by addressing physicians' widespread apprehension of insufficient biosimilar clinical data by providing additional safety and efficacy data. Physicians across Europe, the United States, and Latin America rank peer-reviewed publications, professional society guidelines, and medical conferences as their top sources for biosimilar efficacy and safety information.[6-8,17] Studies show that the source of randomized controlled trial sponsorship (any pharmaceutical treatment) has some to no effect on physicians' confidence in clinical study rigor and findings,[18] and manufacturers should feel empowered to convey valuable information by sponsoring additional clinical studies. Conversely, the least valuable information channels to physicians in these regions include prescribing information, medical science liaisons, and health insurance plans/pharmacy benefit managers.[6-8,17]

THE ROLE OF RWE IN ASSESSING BIOSIMILARS

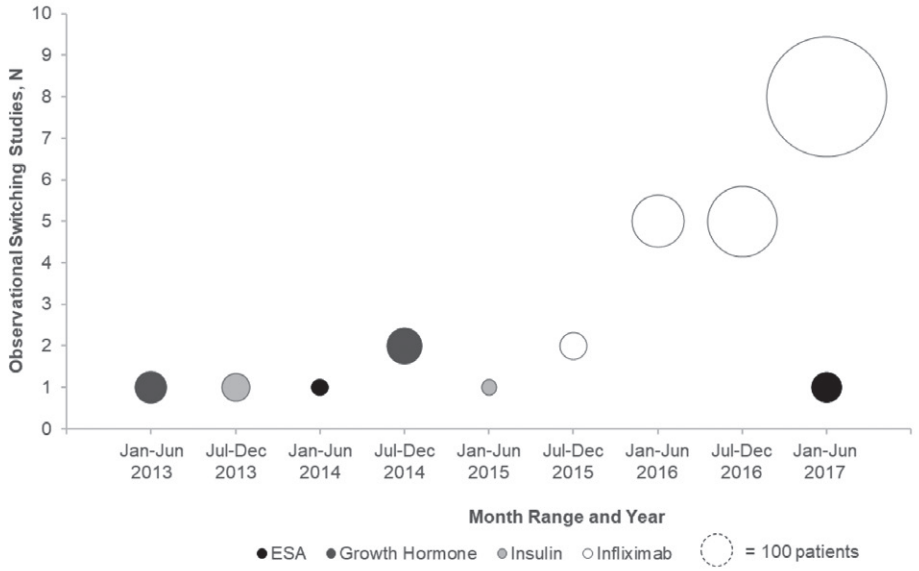
Clinical trials enabling biosimilar approval may provide insufficient evidence to support biosimilar acceptance among all physicians and patients, particularly in less mature markets. Biosimilar registrational randomized controlled trials (RCTs) provide safety and efficacy data, but may be limited by relatively short duration. Furthermore, the resource-intensive nature of RCTs prevents studying every indication in every market. Publishing postmarketing surveillance and other observational studies of real-world data (RWD) offers an important opportunity for manufacturers to provide physicians with additional effectiveness and safety evidence, particularly related to long-term safety, efficacy in extrapolated indications, and effects of switching.

Depending on the study design and objective, RWE studies can follow patients over several years, represent diverse patient populations (including children, elderly, or patients with comorbidities who may have been excluded from registrational RCTs), include patients from extrapolated indications, and focus on specific markets. These studies can also include additional outcomes, such as patient-reported information and economic evidence. Consequently, RWE studies enable generation of safety and effectiveness data demanded by clinicians and cost savings data needed by payers. Furthermore, as more biosimilars are approved, RWE studies may differentiate a single biosimilar from competing biosimilars by addressing outcomes missing in a competitor product. When stakeholders in crowded biosimilar markets perceive a class effect among many biosimilars of the same originator product, RWE studies provide useful distinctions.

DESIGNING AND CONDUCTING RWE STUDIES

Choosing the right RWE study design is critical to generating data that will best address evidence gaps and convince all stakeholders of biosimilar safety and effectiveness, including physicians and patients.[19] Identifying and prioritizing evidence gaps requires market research to determine whether efficacy, safety, immunogenicity, extrapolation, or switching is the most pressing issue, then targeting specific questions within these topics. Each biosimilar must be >

Figure 1: Publication Trends in Biosimilar Switching Studies, January 1, 2013 to June 10, 2017 [1]



Abbreviation: ESA = erythropoietin-stimulating agent. / Note: Bubble size indicates the number of patients.

examined within the context of the indicated population, existing safety and effectiveness data, product maturity, and competitive landscape. For example, prospective observational studies answer key efficacy and safety questions to help build confidence in a newly launched biosimilar, while retrospective studies examining specific populations are useful later in the product lifecycle to answer targeted questions for products with more available RWD.

Conducting RWE studies is usually less resource intensive than operating RCTs, but still may pose a substantial burden to academic groups. Manufacturers should collaborate with organizations capable of generating RWD and groups adept in analyzing, interpreting, and disseminating study findings. One such partner is the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC), a United States nonprofit organization founded by managed care organizations, pharmacy benefit managers, health plans, pharmaceutical companies, and other groups. The BBCIC acts as a neutral convener to support transparent research on biologics/biosimilar safety, effectiveness, and use within populations.[20] Registries for diseases treated with biologics, such as oncology and inflammatory conditions, are also helpful partners in providing manufacturers with biosimilar RWD.

RWE IN BIOSIMILAR LIFECYCLE MANAGEMENT

It is critical that manufacturers work collaboratively with key stakeholders and regulatory agencies to sponsor and disseminate RWE studies on the value of biosimilars. To that end, RWE is an integral aspect of biosimilar lifecycle management. Most RWE studies are conducted postapproval, when launched products are available to diverse populations. These could include postmarketing surveillance of product safety, which is required in some countries, or other studies designed to answer different clinical questions. Hence, RWE is particularly useful as a tool to engage with physicians and patients following product launch until broader familiarity and acceptance of approved biosimilars is achieved. Less mature biosimilar markets should leverage existing RWD from markets with higher initial adoption of a given product to conduct RWE studies.

Although there are only a handful of biosimilars on the market in the United States and limited RWD, the landscape will evolve rapidly as more products are approved and patients gain access to these powerful therapies. There is evidence that an inflection point has been reached in publishing biosimilar RWE (Figure 1).[1] As more biosimilars of the same biologic are developed, switch studies can also address biosimilar-to-biosimilar switching.

CONCLUSION

There are unique challenges for biosimilar adoption in approval and access. Although economic incentives and regulatory frameworks both play important roles within each market, physicians are influential players in biosimilar adoption. Awareness and assurance of biosimilar safety and effectiveness among physicians varies based on market maturity and local experience, but there is a global need for improved communication and dissemination of biosimilar research with physicians. Physicians need more evidence of biosimilar safety and effectiveness—including the effects of switching and effects on extrapolated populations—in high-quality studies reported in peer-reviewed publications. RWE provides useful sources for biosimilar information not captured in registrational trials leading to approval. Biosimilar manufacturers and their collaborators have opportunities to address physicians' concerns by strategically designing RWE studies to fill knowledge gaps in biosimilar safety and effectiveness and increase biosimilar adoption.

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Biosimilar Adoption and Acceptance in Ireland—Still More to Be Done

Gary L. O'Brien, BPharm, MPharm; **Mark Mulcahy, BComm, MSc, PhD**; **Stephen Byrne, BSc (Hon) Pharm, PhD**, University College Cork, Cork, Ireland; **Donal Carroll, BSc (Hon) Pharm**; **Garry Courtney, MB, FRCPI**, St. Luke's General Hospital, Kilkenny, Ireland; **Valerie Walshe, BA, MA, PhD**, Health Service Executive, Cork, Ireland; **Blythe Adamson, MPH, PhD**, Flatiron Health, New York, USA

KEY POINTS

There was a significant time lag between regulatory approval and clinical acceptance of biosimilar infliximab CT-P13 in Ireland.

In this example from an Irish teaching hospital, the introduction of the biosimilar first to new patients, along with a switching study executed in parallel, helped to raise prescriber confidence.

Increased biosimilar medicine usage is of benefit to all stakeholders including patients, prescribers, healthcare payers, and manufacturers.

BIOSIMILAR OPPOSITION

In 2014, 6 of the top 10 blockbuster medicines were monoclonal antibodies. In recent times, small-molecule chemical entity (SMCE) blockbuster drugs like Viagra® (sildenafil citrate) and Lipitor® (atorvastatin), have been superseded by blockbuster biologics such as Humira® (adalimumab) and Enbrel® (etanercept), demonstrating the newly acquired prominence of biological medicines. However, these large-complex proteins (comprising or derived from living cells or organisms) are more complicated than traditional SMCEs due to their unique manufacturing process. Unlike generic drugs of SMCEs, biosimilar medicinal products (biosimilars) which aim to replicate originator biologic products, have given rise to concerns related to their pharmaceutical quality, safety, and efficacy. For this reason, biosimilars are not considered exact replicas of originator biologic medicines. While this uncertainty can prevent physicians from using biosimilars, this is not a problem for generic drugs of SMCEs. Therefore, knowing when it is most appropriate and timely to implement biosimilars into routine clinical practice can be difficult. In September 2014, a large acute teaching hospital was the first in Ireland to introduce biosimilar infliximab CT-P13 in place of originator brand infliximab (Remicade®), to treat inflammatory bowel disease (IBD).[1] The independent systematic evidence base behind the decision-making process used to introduce biosimilar infliximab in this hospital is one example of how healthcare professionals (HCPs) overcame biosimilar opposition.

> Work that aims to enhance the understanding of biosimilar medicines among stakeholders and to encourage best practice of biosimilar use is being conducted by a collaborative organization of various interested parties.[10]

IRISH CASE STUDY

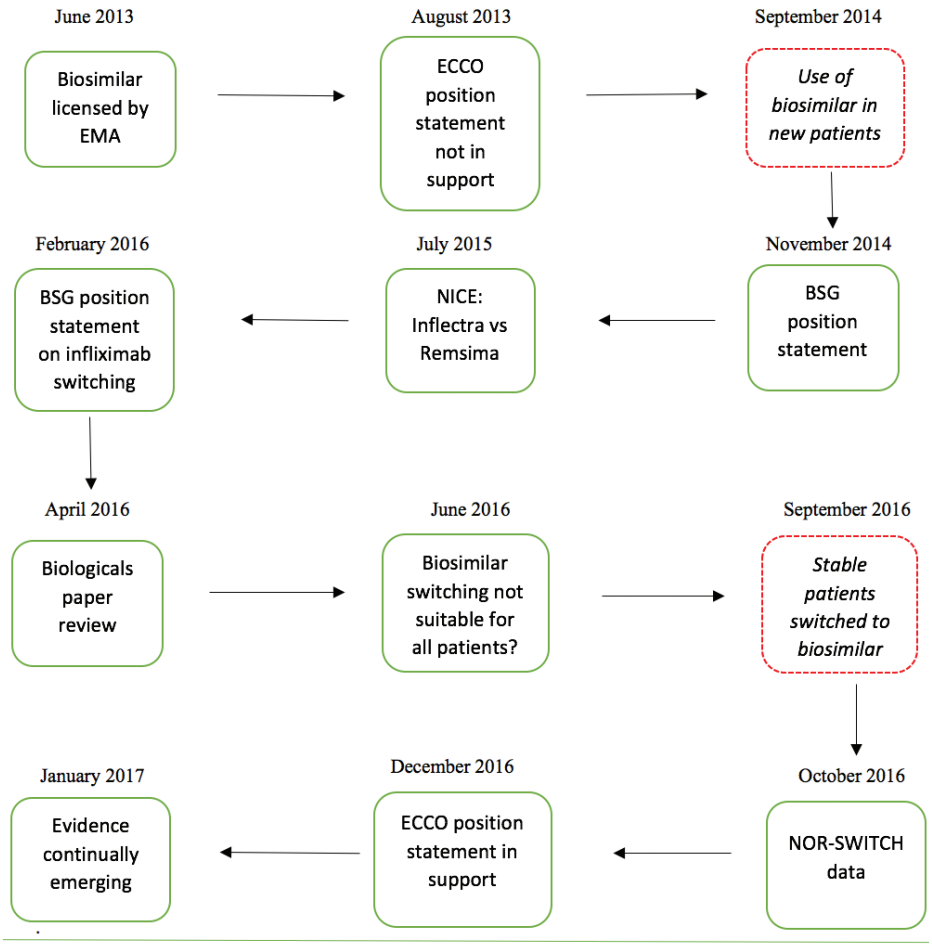
In June 2013, biosimilar infliximab CT-P13 was granted marketing authorization by the European Medicines Agency (EMA) for the same indications as Remicade®. A few weeks afterward, the European Crohn's and Colitis Organisation (ECCO) released a position statement articulating that the use of most biosimilars in patients with IBD should require testing in this particular patient population with comparison to the appropriate innovator product Remicade®, before approval.[2] Contrary to this guidance from the ECCO, the chief pharmacist and consultant gastroenterologist of a large acute Irish teaching hospital decided to introduce biosimilar infliximab CT-P13 for use in new patients in September 2014. Although this new prescribing practice could have been deemed hasty, the British Society of Gastroenterology (BSG) released a position statement 2 months later with updated guidance justifying the introduction of biosimilar infliximab CT-P13 in the clinical setting. During the summer of 2015, the National Institute for Health and Care Excellence (NICE) remarked positively on the topic of biosimilar prescribing. Their report concluded that the EMA was content that the pharmacokinetics, efficacy, safety, and immunogenicity profiles of biosimilars were similar to those of the originator products and concluded that the recommendations for infliximab could apply both to the originator product and its biosimilars.[3]

In February 2016, the BSG updated their previous guidance stating that there was sufficient evidence to recommend that patients who were in stable clinical response or remission on Remicade® therapy, switch at the same dose and dose interval to biosimilar infliximab CT-P13. Despite the position statement from the BSG, this large acute Irish teaching hospital judged that it was premature to switch all of its patients from Remicade® to biosimilar infliximab >

CT-P13. Two months later, a review published in *Biologicals* journal concluded that while prudent switching practices should be employed, growing safety experience accumulated thus far with infliximab CT-P13 and other biosimilars was favorable and did not raise any specific concerns.[4]

In June 2016, *ScienceDaily* published a research article on its website, "Biosimilar switching not suitable for all patients,"[5] based on a study conducted in Spain.[6] At first, the consultant gastroenterologist and chief pharmacist of the hospital thought that this article would counteract previous evidence in favor of switching. However, when examined closely, the study results showed that when antidrug antibodies develop in response to Remicade®, these antibodies also cross-react with biosimilar infliximab CT-P13 as both biologics share structural properties. These findings suggested that antibody-positive patients being treated with Remicade® should not be switched to biosimilar infliximab CT-P13 since these antibodies would also interact with the biosimilar and potentially lead to a loss of response. Despite its misleading title, the results of the Spanish study actually emphasized the similarities between the originator and biosimilar brands of infliximab and reinforced the science behind the safety of switching. At this point, the chief pharmacist and consultant gastroenterologist decided to switch all patients from originator brand infliximab to biosimilar infliximab CT-P13, commencing in September 2016. In October 2016, explorative subgroup analyses of patients with IBD in the NOR-SWITCH study showed similarity between patients treated with originator infliximab and biosimilar infliximab CT-P13 with regard to efficacy, safety, and immunogenicity (The NOR-SWITCH study was one of the first large-scale controlled studies where biosimilar infliximab CT-P13 was tested in patients with IBD).[7] In December 2016, the ECCO released an updated statement revising previous guidelines. One of its prominent recommendations was that switching patients with IBD from the originator brand to a biosimilar product was now deemed acceptable. In this rapidly moving field, the evidence continues to grow supporting the case that biosimilar infliximab CT-P13 is just as safe and effective as the originator biologic (see Figure 1).

Figure 1. Independent systematic evidence base behind the decision-making process to implement biosimilar infliximab CT-P13 in a large acute Irish teaching hospital for the treatment of IBD.



BSG=British Society of Gastroenterology; ECCO=European Crohn's and Colitis Organisation; EMA=European Medicines Agency; IBD=inflammatory bowel disease; NICE=National Institute for Health and Care Excellence. Source: Reference [1].

REGULATORY APPROVAL VERSUS CLINICAL ACCEPTANCE

The decision to treat new patients with and switch existing patients to biosimilar infliximab CT-P13 in this large acute Irish teaching hospital was a multifactorial one underpinned by a robust and extensive evidence-based trial that ultimately convinced prescribing physicians. Biosimilar infliximab CT-P13 was first licensed in June 2013, but prescribers decided to switch patients approximately 3 years later (September 2016). It is therefore evident that there was a significant time lag between regulatory approval and clinical acceptance. In fact, Ireland has the second lowest record of biosimilar use because of Irish HCPs' slow acceptance of biosimilars.[8,9] This is possibly due to a lack of confidence, unwillingness, or knowledge to prescribe biosimilars that is also seen in other European countries. Work that aims to enhance the understanding of biosimilar medicines among stakeholders and to encourage best practice of biosimilar use is being conducted by a collaborative organization of various interested parties.[10]

INTERCHANGEABILITY STATUS

Flixabi®, biosimilar infliximab SB2, received market authorization approximately 3 years (April 2016) after biosimilar infliximab CT-P13. Given its late entry to the Irish market relative to biosimilar infliximab CT-P13, it has been unsuccessful in penetrating this market so far. The chief pharmacist and consultant gastroenterologist of this hospital note that

Table 1. Areas Under Investigation in the Drafting of the Irish Biosimilar National Policy

Prescribing and Interchangeability	By focusing on the remit of biological medicine prescribing, it is hoped that the low uptake of biosimilars in Ireland can be increased
International Biosimilar Medicines Policies	International policies are being examined to decide which policy, if any, could be implemented in the Irish context
Education and Support	Educational programs and support are being researched from the perspectives of the patient, healthcare professionals, and pharmaceutical suppliers
Incentives and Disincentives	Incentives such as gain-sharing agreements and disincentives like patient copayment systems are being analysed
Tendering and Pricing Policies	Internal and/or external reference pricing arrangements as well as the various types of tendering processes used in different countries are being probed for their suitability in the Irish setting
Prevention of Inappropriate Business Practices	In addition to inappropriate business practices previously highlighted, exploration of such professional misconduct is underway

they would not be comfortable switching patients from biosimilar infliximab CT-P13 to biosimilar infliximab SB2 without conducting a comprehensive review of all available evidence, especially evidence from a switching study. This demonstrates that HCPs do not believe that all biosimilars should be subject to the same introduction process into the clinical setting.

IRISH BIOSIMILAR NATIONAL POLICY

The Irish Department of Health (DoH) is in the process of developing a national biosimilar medicines policy which aims to increase biosimilar use by creating a robust framework where biologicals and biosimilars can be used safely, cost-effectively, and confidently in the health service. It is hoped that this policy will address the inter-hospital variation to biosimilar medicine implementation between this teaching hospital and other secondary care settings in Ireland. Table 1 reveals some of the other topics of interest in this policy that are being considered.

COST SAVINGS

Too much money is spent on originator biologics when there are cheaper, equally effective alternatives available. Only 11 biosimilars are currently reimbursable by the Irish healthcare system. This is a concern as over €200 million is spent each year on biologic drugs that already have approved biosimilars or that will have available biosimilars in 2018. It is clear that the potential cost savings from using biosimilars instead of biologicals can be reinvested to increase patient access to other new medicinal products.

REFERENCE PRICING OF ORIGINATOR BIOLOGICS

Reference pricing of biologic products would increase biosimilar usage. Reference pricing of SMCE medicines has already resulted in savings of millions of euro in the Irish primary care setting. This was a powerful initiative to enforce generic substitution of these medicines. In addition, since pharmacists can legally substitute SMCE medicines, Ireland enjoys a high level of generic SMCE medicine market infiltration.

THE PATIENT VOICE

The Irish Platform for Patient Organisations, Science and Industry (IPPOSI) is a patient-led organization in Ireland that works with patients, government, industry, science, and academia to put patients at the heart of health policy and innovation. Its strategy aims to smooth the pathway for new treatments and technologies for unmet medical needs, but it is are also involved in other areas of health like that of biosimilars. In 2017, on behalf of the patients of Ireland, IPPOSI submitted a positive response to the public consultation on the Irish biosimilar national policy. In addition, the Health Products Regulatory Authority (HPRA) in Ireland has launched patient-specific guidance in the form of a leaflet, *Biological and Biosimilar Medicines: What Patients Should Know*, in conjunction with an educational video.

KEY MESSAGE

Undisputedly, increased biosimilar medicine usage is of benefit to all stakeholders: increased access for patients, more treatment options for prescribers, sustainable healthcare budgets for payers, and more business opportunities for manufacturers.

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Predicting Market Outlook: Enhancing Market Forecasting via Application of Pharmacoeconomic Modeling Techniques

Baris Deniz, Senior Research Scientist, Modeling & Simulation, Evidera, Bethesda, MD, USA

KEY POINTS

Traditional stock and flow models have significant limitations when applied to complex and evolving markets, as they get unwieldy when needed to account for segmentation of the market based on patient characteristics, treatment history, patient preferences, or disease stage.

Pharmacoeconomic models are well suited to address limitations associated with stock and flow models, and they can improve the quality of market outlook predictions.

Within the health economics community, there is a wealth of scientific experience and know-how in the development of the analytical frameworks to address a wide range of research questions that also can be used to help improve the quality of forecasting models.

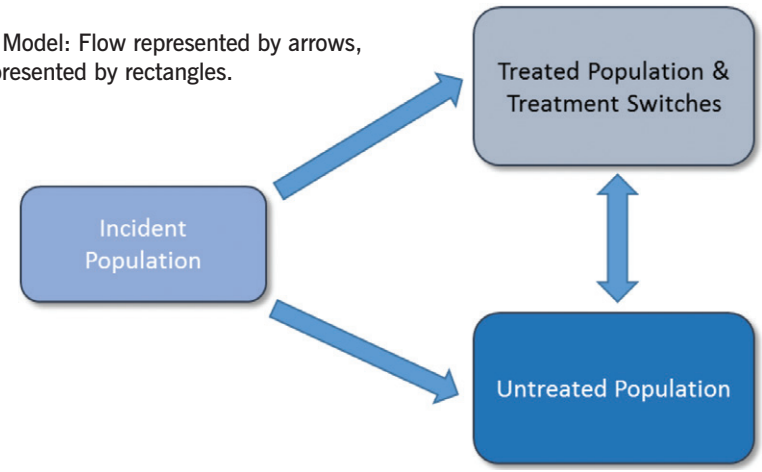
Models are tools to help understand complex systems through analytical frameworks. Hence, all models are implicitly an approximation to the reality, rather than a replica. That said, it is also important to keep in mind that the utility of a model is still highly dependent on how the reality is conceptualized and translated into an analytical framework. This can be a critical nuance, especially if results from a model are used to inform decisions that have substantial implications, such as reimbursement decisions for new therapies or budget and resource allocations across biotechnology and pharmaceutical organizations. Therefore, while all models are approximations, the required level of approximation should be considered and assessed carefully, as it may have significant consequences through the decisions they inform.

The organizations typically use mathematical models to optmize investment decisions by forecasting the market outlook in a given therapeutic area, and use model-produced results to inform both short- and long-term strategies. These strategic choices often have material implications on how organizations structure themselves and allocate their resources. The typical approach to conducting market forecasting has been to use stock and flow (S&F) models that conceptualize the market in relatively straightforward terms such as key patient segments, anticipated market changes, etc. However, as the health care markets evolve and new treatment options continue to become available at an unprecedented rate, traditional simplistic approaches to understanding market evolution may not be sufficient, as they often fail to capture nuances in increasingly complex markets, such as more detailed patient segmentation based on the patient preference and behavior and medical histories. More often than not, such critical market nuances are either over-simplified or ignored for the sake of low computational burden which, however, increases the risk of lowering the quality of predicted power. Hence, it may lead up to strategic decisions that are based on limited, or in some cases, wrong market expectations.

CONVENTIONAL APPROACH TO MARKET FORECASTING: STOCK AND FLOW MODELS

The concept of S&F goes back to the late 19th century,[1] where initially it was applied to problems in economics. In the original approach, the term "stock" referred to variables that do not have a time dimension and therefore can be measured at a given point in time, whereas the term "flow" represented the change in "stock" measured for a given time interval. When applying S&F models to market forecasting, the stock represents the size of each of the patient segments of interest, such as incident patients, diagnosed but untreated patients, or patients receiving certain treatments. The flow represents the

Figure 1: S&F Model: Flow represented by arrows, and stocks represented by rectangles.



rates at which patients move between defined stocks over time. The flow is usually dependent on market dynamics and events, such as market uptake of a therapy following its launch, the rate of diagnosis, treatment discontinuation rates, etc. (Figure 1). Using such estimates based on patient dispositions, this type of analysis provides insight into the anticipated evolution of the market regarding the size of the patient segments, and helps organizations identify future commercial opportunities and risks.

S&F models are simple to construct and are appropriate for markets where there are a limited number of variables and dynamics to consider. However, these models have limitations, which become more apparent in more complex market scenarios. S&F models may become harder to construct and manage when there are multiple key market dynamics, such as the impact of patient or physician preference on treatment selection, or when patient's age, sex, race, treatment history, disease activity, the location of service, etc. are important factors determining how patients may be managed in clinical practice. In such scenarios, the application of S&F models either becomes too complicated and loses transparency, or requires numerous assumptions to be able to approximate the reality into the simple framework.

Understanding market evolution is critical in ever-evolving and highly competitive healthcare markets. Therefore, to ensure the development of reliable strategies, it is necessary to employ flexible, sound modeling approaches that can capture the inherent complexity of the field.

AN ALTERNATIVE APPROACH: PHARMACOECONOMIC TECHNIQUES APPLIED TO MARKET FORECASTING

Pharmacoeconomic evaluations are tools designed to inform decisions to improve healthcare delivery and health outcomes.[2] Typically, such decisions require the development of analytical models to better understand short- and long-term health and economic consequences of new interventions compared to existing alternatives. This is especially important in the absence of long-term evidence from randomized clinical trials and/or head-to-head comparison of therapies in a trial setting. It requires a solid understanding of the interactions between key disease and management concepts: the epidemiology of the condition, natural disease progression, efficacy and safety profiles of therapies, treatment pathways, and pharmaceutical and medical costs associated with the management of the condition. This is, indeed, a much broader set of considerations than what S&F models would take into account for typical market forecasting.

When applied to market forecasting, pharmacoeconomic models can still use the same building blocks of traditional S&F market forecasting models (see Figure 2), but with greater flexibility that can help capture additional details around each concept, which in return can help address inherent challenges of S&F models.

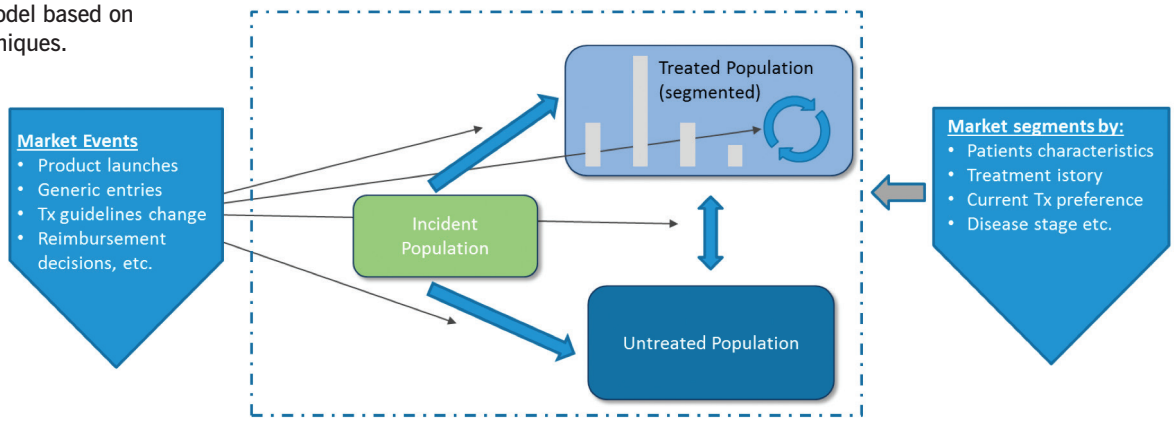
Market forecasting using pharmacoeconomic techniques relies on 3 concepts:

- **Market segments** that describe the patient populations of interest, which can be defined not only by the treatment that patients are on at a given time, but also other key variables such as treatment history, age, sex, race, underlying disease activity, etc. The size of each market segment is monitored throughout the simulation to represent how it may change over time. The advantage of the pharmacoeconomic technique is that it captures the complexity of the market segments using any relevant combination of descriptors, which can very quickly become unmanageable with a S&F model.
- **Patient flow** is the same as what it represents in a S&F model; that is the rate at which patients move between market segments. However, with pharmacoeconomic techniques, patient flows can be defined in greater detail for each market segment (eg, line of therapy, treatment history, disease activity, etc) so that market nuances and their impact on rates at which patients move can be reflected in the model framework.
- **Market events are** disruptions in the existing market dynamics that impact the rate of patient flow and hence impact the size of market segments. Examples of market events include the introduction of new therapies, changes in clinical treatment guidelines, or changing patient/physician preferences over therapy profiles (eg, mode of administration or efficacy/safety profile).

EXPLORATION OF UNCERTAINTY: SENSITIVITY ANALYSIS

Sensitivity analysis is an essential aspect of modeling, because it allows one to understand the uncertainty associated with the model inputs and the structure, hence the model results. S&F models typically address uncertainty in a fairly simplistic way; in addition to the base case, optimistic, and pessimistic sets of assumptions >

Figure 2: Forecasting model based on pharmacoeconomic techniques.



regarding the market events (eg, uptake of new products and other key model parameters). This approach is known as scenario analysis because it compares alternate scenarios that are constructed based on analyst expectations around how the market may evolve. However, pharmacoeconomic models are typically developed to employ 2 additional techniques that allow for a more sophisticated and rigorous assessment of parameter uncertainty, namely deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). In DSA, each of the parameters of the model is varied one by one to both a low and a high plausible value, and the primary model outcome is evaluated with the new value. Then all of the parameters are ranked in terms of the impact on the primary outcome, and their effects are presented in a way that identifies the key parameters that have the largest impact on the outcome. In PSA, all of the parameters are varied simultaneously, drawing each parameter stochastically from a distribution, and the model outcome is evaluated for each parameter set. The scatter of outcomes is then plotted on a plane in order to give an assessment of the total parameter uncertainty in the model. Together, the tools of DSA and PSA, which are standard components of pharmacoeconomic analysis, provide much richer insight into the uncertainty of the model results than simple scenario analysis.

CASE EXAMPLE: COMPARISON OF S&F WITH THE PHARMACOECONOMIC APPROACH

To demonstrate the differences of the 2 aforementioned methods, we applied each method to a hypothetical problem, where we tried to predict the market outlook over the next 5 years for a slow-progressing chronic disease state. The example included the following specifications:

• **Available Therapies:** Three established therapies (E1, E2, and E3) are available in the market with varying efficacy, safety, and convenience profiles (Figure 3).

• **Patient Preference:** Patients prefer therapies with favorable safety/convenience profiles at earlier stages of disease management and trade off safety for efficacy as they progress on their treatment pathway.

• **Market Events:** Two new therapies, N1 and N2 are expected to launch in year 1 and year 2, respectively. The new treatments have the following profiles:

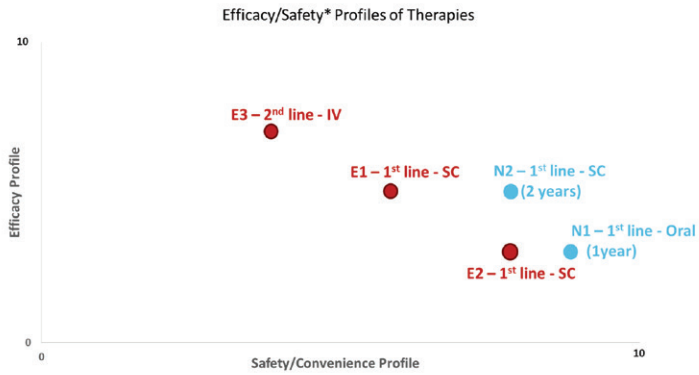
a) N1 improves the safety/convenience profile of E2, and at the same level of efficacy with E2;
b) N2 improves the efficacy profile compared to E2 and the safety profile compared to E1.

The new therapies are expected to impact the current market dynamics by offering new safety/efficacy trade-off options for the patients and physicians. The key questions of interest are:

- What would be the market share of each new therapy over the next 5 years, and
- What will be the magnitude of the change in the market share of each established therapy?

The key difference between the 2 models is that, the S&F model assumes that certain percentage of patients from each segment will "flow" (ie, switch from the segment) annually and the switching population will be distributed between other segments based on pre-determined ratios determined by the analysts. To illustrate the simplicity of the model, the S&F model does not track or account for patient preferences and/or medical histories (eg, previous treatments

Figure 3: Representation of the efficacy/safety/convenience profiles of the available (E1, E2, E3) and new (N1, N2) treatment options.



*Higher value on the efficacy and safety/convenience scale means more favorable profile. / Abbreviations: IV = intravenous infusion; SC = subcutaneous injection.

Table 1: Key differences in the case study among S&F and pharmacoeconomic-based models

S&F Model	Pharmacoeconomic Model
Stocks • Treated patients (by therapy) • Untreated patients	**Market Segments defined by** • Treated patients (by therapy) • Patients' treatment history • Untreated patients
Flows • Treatment switches • Incident patients • Treatment discontinuation • Death	**Patient Flow** • Treatment switches due to 1. Efficacy 2. Safety • Incident patients • Treatment discontinuation • Death
Market Events • New product launches	**Market Events** • New product launches

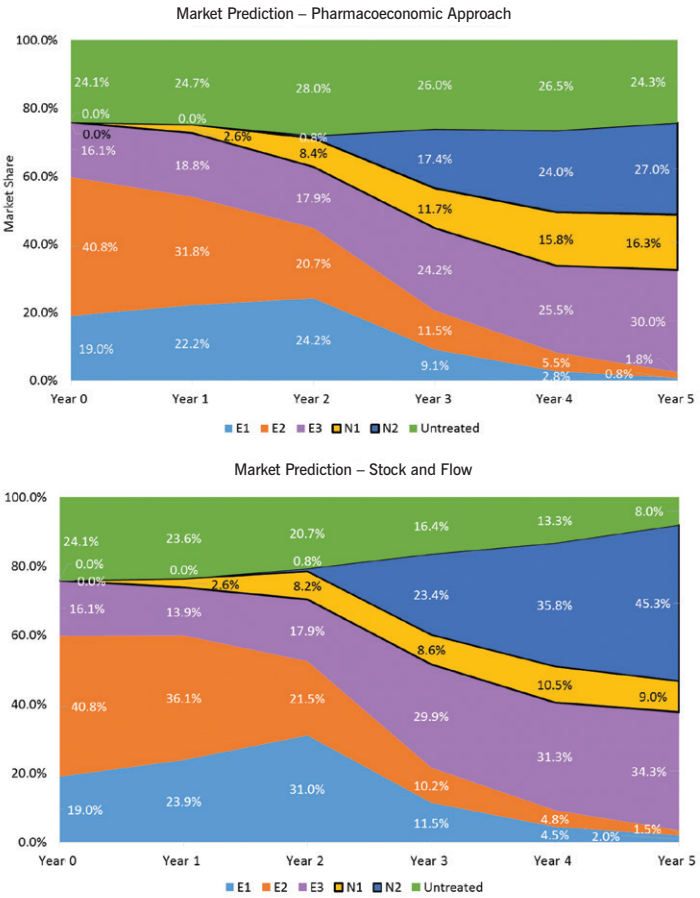
patients have been on), hence the market segments patients are assumed to join after leaving the previous segment does not play a role in determining the next segment. On the other hand, while it uses the same flow rates market segments as the S&F model, the pharmacoeconomic model tracks the patient preference and medical history, and determine the next segment a patient may join based on these considerations. More specifically, in the pharmacoeconomic model:

- Patients cannot go back to a therapy that they tried in the past, assuming that the reason for the original discontinuation still holds true.
- Patients who switch due to efficacy cannot be assigned to a therapy with the same or lower efficacy score, and
- Patients who switch due to safety/convenience cannot be assigned to a therapy with the same or lower safety/convenience score.

RESULTS FROM GROWTH

When we forecasted the growth of the market in this hypothetical disease using each of the models, there were substantial differences in the market outlook predictions (Figure 5). The S&F model estimated that the launch of N2 in year 2 would bring a majority of

Figure 5: Comparisons of market evolution results using the pharmacoeconomic model (A) an S&F model (B)



E1-E3: existing therapies, N1-2: new therapies.

untreated patients back into the market and will be used for their treatment, thus becoming the market leader by reaching a market share of 45% by year 5 in the model (Figure 5B). In contrast, the pharmacoeconomic-based model suggested that, while N2 would grow rapidly initially, by year 5 it would reach a market share of only 27%, which is less than the share of E3 (ie, 30%) at that time (Figure 5A). Its impact on bringing untreated patients back to the "treated" segment is estimated to be more moderate than the S&F model. Furthermore, while the S&F model predicted small growth for N1 with a market share of only 9% at year 5, the pharmacoeconomic-based model predicted more steady growth, reaching 16%.

IMPLICATIONS

Considering the questions set at the beginning, the results of the 2 models can lead to substantially different strategic choices due to differences on the expectations of market evolution. For instance, based on the pharmacoeconomic model, one of the considerations can be further investing in mobilizing the untreated patient population, as a third of the market is expected to remain "untreated" over the next 5 years. Whereas the S&F model would suggest a limited return of investment in such an activity, as new product launches would bring them to the "treated" segment anyway. Furthermore, based on the expected growth of N1 or N2, prioritization and level of investment towards either of the new therapies could differ by respective manufacturers, such as the size of the salesforce to hire for a particular product.

As can be seen from this simple example, while the direction of the results from both models is similar (ie, new therapies grow in market share, whereas existing therapies lose share), the magnitude of changes are substantially different, which can lead to significantly different strategic choices. Such examples of diverging implications based on future expectations can be expanded. Pharmacoeconomic models include all of the same capabilities as S&F models, but are more flexible and allow for more interaction between key variables. Given that markets are known to be highly complex and that models inform important investment decisions, it is reasonable to use a sophisticated tool that can more closely approximate the dynamic complexities of the market and explore scenarios in an interrelated way. While it would be unreasonable to expect that the market will behave exactly the same way that either of these models predicts—it is important to keep in mind that all models are approximations to the reality—how market dynamics are conceptualized and captured is key in conceptualizing the market dynamics as they may lead to substantially different conclusions and strategic choices.

CONCLUSION

Healthcare markets are changing at an unprecedented rate and planning for future market conditions has become critical for ensuring that organizations are prepared for what the future may hold. As markets evolve, they are becoming more nuanced and segmented, meaning that market outlook projections using traditional simplistic tools will no longer be adequate to inform strategic decisions. Pharmacoeconomic models employ well-established and validated methods, and are utilized to address complex questions. Within the pharmacoeconomics and outcomes community there is a wealth of scientific experience and know-how in the development of such analytical frameworks to address a wide range of research questions, which can also be used to help improve the quality of forecasting models. Given the increasing importance of such tools for decision-making purposes and evolving market complexities, pharmacoeconomic modeling methods can also be used to address this growing vital need.

Pharmacoeconomic models offer a sophisticated set of tools that allows for a more detailed representation of complex market dynamics, which can aid in making important strategic decisions via better understanding and hypothesizing how healthcare markets may evolve over time.

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Additional information

The preceding article is based on a workshop given at the ISPOR 21st Annual International Meeting.

To view Dr. Deniz's presentation, go to: https://www.ispor.org/Event/ReleasedPresentations/2016Washington#workshoppresentations

Understanding Productivity Benefits and Related Future Research Needs in Cost-Effectiveness Analysis

Anirban Basu, PhD, University of Washington, Seattle, WA and the National Bureau of Economic Research, Cambridge MA, USA

KEY POINTS

Productivity is an important effect of a health intervention.

Second Panel on Cost-Effectiveness Analysis provides guidance on how to measure and value productivity effects.

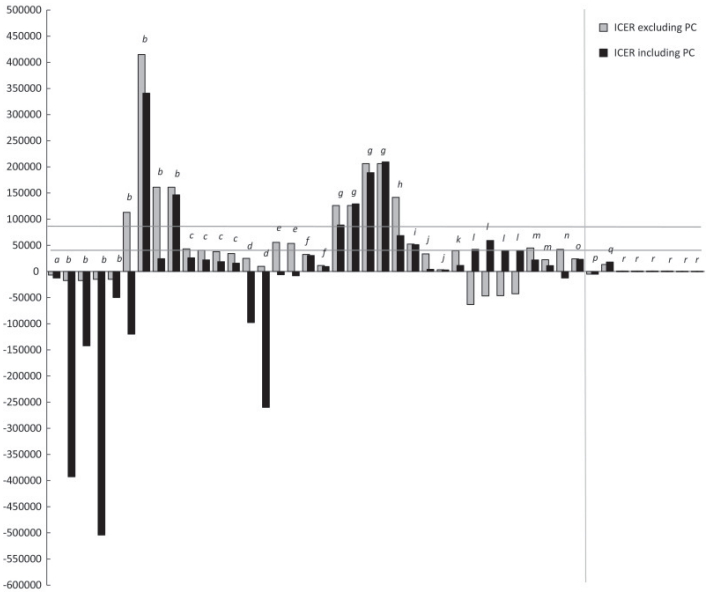
Many payers within the United States may be interested in knowing about these effects.

Healthcare can have a profound impact not only on the health-related well-being of an individual but also on one's functional status, which impacts the ability to contribute to society positively. One such important manifestation of changed functional status is its effect on productivity or the production of goods in a society, which are valued by others. When economic evaluation of healthcare interventions are conducted from a societal perspective, these benefits or costs should be accounted for through productivity estimates. The First Panel on Cost-Effectiveness in Health and Medicine [1] had recognized the importance of these benefits and recommended that they should be part of the calculus in establishing the societal benefits of an intervention. However, the panel concluded that these benefits are captured through stated preferences of the health state valuation such as quality-of-life weights. Hence, any explicit measurement of these benefits beyond quality-adjusted life years (QALYs) would lead to "double counting".[2,3]

Empirical evidence since the First Panel, however, shows that QALYs typically do not reliably capture measures of productivity. [4-7] In most cases, productivity effects are simply not considered by the respondents to preference elicitation questions,[8] and sometimes they are explicitly asked to ignore them.[9] Researchers had long recognized this limitation of QALYs and had started incorporating explicit productivity estimates in CEA done from a societal perspective. Incorporating these estimates often has been found to have profound effects on the incremental cost-effectiveness ratios (Figure 1). Based on this long line of evidence, the Second Panel on Cost-Effectiveness in Health and Medicine [10] concluded that QALYs are meant to reflect only a measure of health, and the productivity effects should be explicitly

> QALYs are meant to reflect only a measure of health, and the productivity effects should be explicitly measured and accounted for in the numerator of an incremental cost-effectiveness ratio from a societal perspective.

Figure 1: ICERS with and without productivity costs. Reproduced from Krol et al. [8].



measured and accounted for in the numerator of an incremental cost-effectiveness ratio from a societal perspective.

Productivity benefits are also becoming an important part of promoting value calculations in healthcare.[12,13] In fact, the notion of "patient-focus" put forth by many private healthcare plans in the United States highlights the need for considering productivity benefits.[14]

WHAT SHOULD BE MEASURED

Productivity is viewed typically as a measure of efficiency and, therefore, must net consumption from total production of individuals. Total production may come from labor production, informal labor market production, and household production. Each of these production types could be affected by health and healthcare intervention. Additional income coming from governmental welfare, such as disability payments, is not considered to have any production value as this is merely a transfer of income from one person in the society to another. Similarly, investment income represents the flow of money from fixed assets and is unlikely to be affected by health or survival, and therefore should not be considered as production. Consumption, on the other hand, can occur from any of the income sources, including welfare payments and investment income, and also would likely vary by health status. Therefore, for any given period in the future (suppressing notation for discounting), the total productivity measure is given as

$$S(H)\cdot[(L(H) + IL(H) + HP(H) - C(H)]$$

Where

H = Health; (H) = indicates dependence on health
S = survival to that specific period
L = Labor production
IL= Informal labor production
HP = Household production
C = Total consumption, and

Changes in health $\triangle H$, presumably brought about by an intervention, generate two separate effects, one through a change in productivity and the other through a change in survival, $\triangle S$.

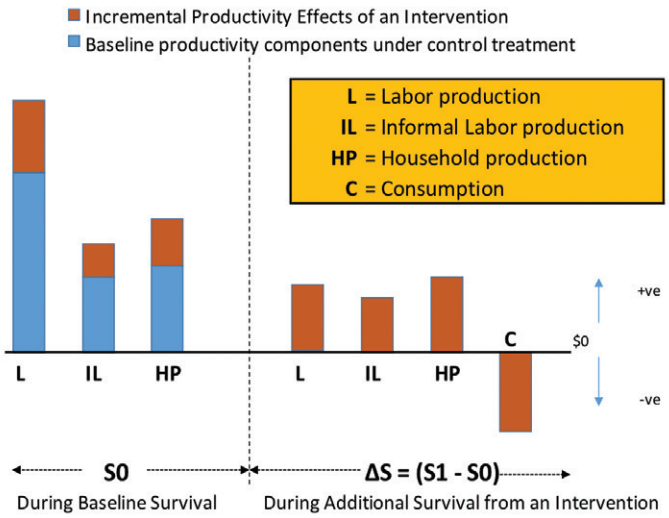
$$S(H)\cdot[\triangle L(\triangle H) + \triangle IL(\triangle H) + \triangle HP(\triangle H) - \triangle C(\triangle H)] + \triangle S(\triangle H)\cdot[(L(H) + IL(H) + HP(H) - C(H)]$$

The first term shows the changes in productivity due to changes in health, conditional on survival, and includes changes to labor production $\triangle L(\triangle H)$, informal labor production $\triangle IL(\triangle H)$, and household production $\triangle HP(\triangle H)$. It is important to note that overall productivity changes typically nets out changes in consumption due to health, $\triangle C(\triangle H)$, from the changes to production. However, in cost-effectiveness analysis, one can **ignore** the changes to consumption due to changes in health and hence $\triangle C(\triangle H)$ is highlighted in red. This is because if one considers changes to consumption, one must also consider changes to the utility or well-being brought about by the changes in consumption (Nyman 2004).[15] However, since CEA focuses on maximizing health through QALYs, there is no scope for measuring changes to overall well-being due to the changes in consumption. Fortunately, economics comes to the rescue. It has been shown, through the famous Envelop theorem in economics, that the value of the utility change due to consumption change is equivalent to the magnitude of the consumption change at the margin.[16] Therefore, ignoring both those factors would not change the optimality condition for investment in health. Consequently, in CEA, one can ignore these changes to consumption brought about by changes to health.

The second term, often dubbed as "future costs," reflects the net resource use in the society due to living longer. Here, the net resource use is the difference between the absolute levels of production from the three sources and total consumption.

Thus, the total productivity effect of an intervention in CEA is illustrated in Figure 2. Interventions that do not produce any survival gains would only focus on the first part of the productivity effect.

Figure 2: Components of incremental productivity effects.



HOW TO MEASURE AND VALUE COMPONENTS OF PRODUCTIVITY EFFECTS

The Second Panel recommends valuation of production effects from a societal perspective using a human capital approach. The rationale for using this approach over alternatives such as the friction cost methods is detailed in the Second Panel Report.[4,10]

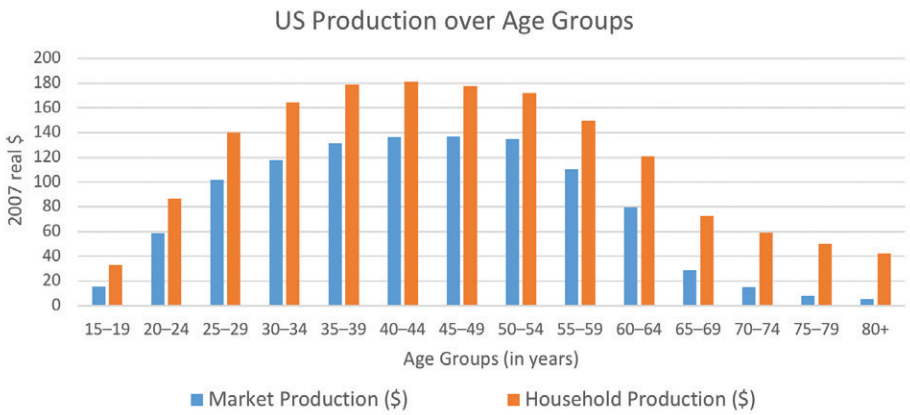
LABOR MARKET PRODUCTION

Labor market production refers to earned income in a formal job. Health certainly influences the ability to participate and perform in the labor market. In prospective evaluation studies, standard questionnaires exist to capture labor market participation and earned income. In many cases, a period-specific average number of hours of participation in the labor market can be imputed based on the product of the following 2 parameters: (1) the health-status–specific likelihood of a person's participating in the labor market during that period, and (2) the health-status–specific number of hours worked if participating in the labor market. Because an individual would be employed in the market only if the marginal product of labor is at least as large as the wages plus fringe benefits offered, the marginal value of a unit of time in the formal labor market is given by the (pre-tax) wages plus fringe benefits. In 2014, the average fringe rate in the United States was 46% (Bureau of Labor Statistics [BLS] 2015). Age-specific and average wages in the United States can be found in the BLS website. >

INFORMAL MARKET PRODUCTION

Informal market production involves participation in productive activities without being paid formally. For informal market production, one should only consider activities outside the household to differentiate from household production. Such production includes volunteering time for various activities (eg, babysitting), counseling, and mentoring younger people.[17,18] For example, an emeritus professor who is no longer on the payroll of a university may still spend a large number of productive hours mentoring students. To the extent that health status can enable one to participate in these activities, which in essence is thought of as replacing one's leisure time, these hours should be valued as productive time. More research is needed in measuring the impact of an intervention on informal market production. Many validated questions from the American Time Use Survey (ATUS, https://www.bls.gov/tus/) may be used to measure this form of productive time prospectively. Time spent in informal markets should be valued the same way as time spent in formal labor markets.

Figure 3: Labor market and household production over age in the United States



Source: Grosse et al. 2009.[19]

> Failing to value productivity benefits of health interventions could be stark for low- and middle-income countries, where growth in labor productivity play an important role in economic development.

HOUSEHOLD PRODUCTION

Household production represents the sum of time spent doing services around the household and time spent caring and helping household children and adults.[19] It has the same rationale for inclusion as informal market activities; only that household production consider unpaid productive activities within the household. Grosse et al [19] provide estimates for the labor market and household production in the United States by age and gender. Figure 3 presents both labor market and household production for the US population over age groups. The fact that household production, on average, is higher than labor market production at all ages and that the former reduces more slowly over age than the later indicates the importance of accounting for household production and the impact of health on it.

Like informal market production estimates, more research is needed in measuring the impact of an intervention on informal market production. In many cases, informal market and household production can be considered jointly in such prospective evaluations.

CONSUMPTION

As explained in the previous section, accounting for average non-healthcare consumption levels to net them out from total production levels becomes important during the added-years of life with an intervention. These can be estimated from the Consumer Expenditure Surveys in the United States.

CAREGIVER TIME

An important effect of an intervention that alleviates health is on caregiving activities. Time contributed by formal (paid) and informal (unpaid) caregivers in caring for patients should be valued in the same way as productivity costs.[4] Hourly rates for both should be based on the marginal pre-tax wage rate plus fringe benefits observed in the formal caregivers' market.

DISTRIBUTIONAL ISSUES RELATED TO THE INCLUSION OF PRODUCTIVITY EFFECTS IN CEA

Several distributional issues are generated with the inclusion of productivity estimates in CEA. Traditional cost-benefit analysis typically would use targeted productivity estimates, based on age, sex, health status, and other characteristics of patients, to reflect the true resource use in the society. However, such an approach would, for example, imply that interventions meant to alleviate health conditions that are more prevalent among low-income populations would fare worse than other interventions. In contrast, a single national estimate of an hourly wage or average annual salary and annual consumption estimates may be used to value all productive time across all studies. These distributional issues are real and should be directly confronted by any decision maker presented with cost-effectiveness results that only account for 1 input into the overall decision-making process. However, these concerns do not preclude inclusion of productivity estimates in CEA. There are equally important and valid distributional issues even when productivity estimates are not included. Ignoring the productivity costs would bias evaluation in favor of those interventions that have only life expectancy gains, but generate no functional benefits. Failing to value productivity benefits of health interventions could be stark for low- and middle-income countries, where growth in labor productivity play an important role in economic development.[21]

For example, the value of a new drug for people with schizophrenia that improves cognition, which in turn leads to better functional outcomes, including labor market participation, would be seriously underestimated if these productivity benefits were not considered. Quality of life weights have long been subject to ethical issues. In fact, any consistent model for budget allocation would have "unethical" implications.[20] As

the Second Panel points out, the key is to develop a consistent process within an institution to account for effects of interventions on these resources and follow transparent, deliberative processes to address distributional issues.

CONCLUSION

Productivity is an important effect of a health intervention. Consistent measurement of the productivity effects in CEA can help convey the value of many healthcare interventions beyond their effects on health and healthcare resources. Although the inclusion of these effects in CEA would render a societal perspective to such analysis, many payers within the United States, especially those offering employer-sponsored plans, may be interested in knowing about these effects.

ACKNOWLEDGEMENT

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Additional information

The preceding article was based on an issues panel presentation presented at the ISPOR 22nd Annual International Meeting. To view this presentation, go to http://www.ispor.org.

Challenges and Best Practices for the Japan Health Technology Assessment Pilot Program

Finn Børlum Kristensen, MD, PhD, University of Southern Denmark, Odense, Denmark; **Ataru Igarashi, PhD**, University of Tokyo, Tokyo, Japan; **Peter J. Neumann, ScD**, Tufts Medical Center, Boston, MA, USA; **Dana P. Goldman, PhD**, University of Southern California, Los Angeles, CA, USA

KEY POINTS

Health technology assessment (HTA) processes continue to expand globally.

Authorities developing new HTA processes should draw inspiration from the approaches taken by existing HTA bodies, adapted to regional circumstances.

These guiding principles may be helpful for Japan, which is in the process of developing and establishing their own HTA.

To guide health technology policy decisions, countries often rely on health technology assessments (HTAs). HTAs typically involve the evaluation of a medical technology's impacts, but can be operationalized for different purposes, depending on the needs and policies of a country. For decades, countries such as the United Kingdom, Canada, and Australia have used HTAs to inform resource allocation. In the new climate of healthcare cost concerns, a wave of countries without formal HTAs, such as Japan, Costa Rica, and Argentina, are implementing their own processes.

> When not executed according to sound principles, HTA could be viewed skeptically as an attempt to limit patient access to contain costs or a lever for government price negotiation.

For countries developing their own HTA systems, the variability in HTA purpose and structure can make identifying optimal aims and processes challenging. For example, high- and upper-middle income countries tend to use HTA to guide reimbursement and coverage decisions; lower income countries tend to use HTA for planning and budgeting.[1] In this piece, we discuss some common challenges and best practices for burgeoning HTAs to consider, particularly those that may be applicable to Japan, which is completing a pilot of their proposed HTA process. As the third-largest economy in the world, the results and subsequent implementation of Japan's HTA has significant implications for HTA processes around the world.

HTA PILOT PROGRAM IN JAPAN

Japan has the world's longest life expectancy and ranks highly across a number of health metrics. Its universal healthcare system, which provides insurance and comprehensive care to all citizens, has contributed significantly to these health achievements. Like all health systems, however, Japan's system has faced rising healthcare expenditures and budgetary constraints. The Japanese Ministry of Health, Labour, and Welfare's (MHLW) Central Social Insurance Medical Council (Chu-I-Kyo) has developed an HTA process that evaluates drugs and medical devices post-launch based on clinical and economic benefits relative to a comparator.[2]

Launched in 2016, the HTA pilot phase evaluated 7 previously reimbursed drugs and 6 medical devices. The results of the HTA evaluation will be reflected directly by a price revision, but only a portion of the price can be adjusted via the HTA review. Four other factors, including social impact and ethics, may be considered during the appraisal process, each assigned a 5% weight. Although the results of this pilot have not been disclosed publicly, Japan aims to formally launch their HTA in April 2019.

COMMON CHALLENGES FOR NEW SYSTEMS AND PROCESSES OF HTA

The first step in establishing an HTA is to determine the policy decisions that the HTA should inform. These decisions depend on many public health and economic factors, such as healthcare coverage. Since Japan's health system covers all medications, their HTA will inform pricing adjustments. Regardless of the purpose, however, all HTAs face similar start-up considerations.

ESTABLISHING GOOD PROCESSES AND METHODOLOGIES

Creating a new HTA requires developing a scientific framework for evaluating new technologies and a process for conducting these evaluations. Best practices and guidelines continue to evolve as the evidence base grows and new scientific techniques are innovated.[3] However, the core of high-quality economic and policy research remains constant, meaning that HTAs must define the appropriate interventions, populations, comparators, outcomes, and time horizon to ensure the evaluations are appropriate for the relevant policy decisions. The MHLW has commissioned and published guidelines for cost-effectiveness analyses,[2] developed by

Japanese health economists, although the process for feedback and refinement is unclear.

DEFINING A COST-EFFECTIVENESS THRESHOLD

HTAs commonly rely on cost-effectiveness thresholds, or the cost for each additional unit of the outcome where "cost-effectiveness" or reasonable value is anticipated. This benchmark could also be conceived as a measure of the opportunity cost of the health outcomes for the marginal intervention that must be relinquished to provide resources for a new intervention.[4] Typically, quality-adjusted life years (QALY)—a measure of life-extension and quality of life—are used as the unit of outcome.

Since cost-effectiveness thresholds can inform whether a technology has "low" or "high" value, establishing the appropriate value is essential. There are no universally accepted values, but some fall in the range of one to three times gross domestic product (GDP) per capita. In the United States, for example, the conventional willingness-to-pay range has been $50,000 to $150,000 USD, and in the United Kingdom, it has been closer to $25,000 per QALY.[5] In both countries, thresholds may be higher for treatments targeting certain diseases or populations. Japan's currently selected threshold of JPY5M falls within the lower end of the range; however, the function of the threshold could be considered conceptually different as a starting point for price revisions, instead of as a benchmark for coverage decisions.

BUILDING CAPACITY

In addition to the scientific methodology, developing a rigorous HTA also requires identifying and allocating human and financial resources to support the process. Securing and retaining these resources can be challenging, especially for countries without well-established HTA programs.[1] Engaging global experts during the HTA development process can help ensure that human resources are experienced and knowledgeable.

STAKEHOLDER BUY-IN

When not executed according to sound principles, HTA could be viewed skeptically as an attempt to limit patient access or a lever for government price negotiation. Involving a range of stakeholders, such as patients, providers, manufacturers, and scientific experts in the development process can support the credibility of an HTA.

THE HTAS OF TOMORROW

Developing an HTA has the potential to improve public health and societal welfare significantly; however, there is no "one-size-fits-all" approach, due to country-specific needs, resources, and policies. For example, Australia does not use an explicit willingness-to-pay threshold in their decision making and publishes the decisions of the Pharmaceutical Benefits Advisory Committee on the internet without disclosing the details of the economic analyses.[6] The United Kingdom's National Institute for Health and Care Excellence (NICE), while building primarily on drug manufacturers' submissions, often commissions an independent academic center to prepare evaluations for consideration by the technology appraisal committee.[7]

Countries establishing new HTAs, like Japan, have the opportunity to identify components of existing processes that best align with the objectives of their health system. As these processes have evolved globally, so have the needs of the health systems they serve. In the current climate of seeking value and quality in care and making decisions based on a body of evidence, the following practices could be helpful for nascent HTAs.

TRANSPARENT PROCESSES AND DECISION MAKING

Many HTA guidelines recommend transparent processes and decision making for the evaluation of new medical technologies.[1,8] Transparency can ensure appropriateness of the approaches selected, build greater confidence in the results, and allow for greater participation of all stakeholders, including manufacturers, providers, and patients.

REAL-WORLD DATA INCORPORATION

Randomized controlled trials remain the gold standard for evidence of efficacy and safety for new medical technologies. However, there is growing interest in incorporating real-world data, given differences in patient populations and behavior between the controlled setting of clinical trials and the real world.

MULTISTAKEHOLDER ENGAGEMENT

There has also been a growing recognition of the limitations of conventional economic methods to measure the true value of new medical technologies. For example, a treatment's nonclinical benefits, such as reduced caregiver burden and improved productivity, are often not included in standard economic evaluations. Confirming that key stakeholders, particularly patients, are included can help ensure that the full benefits of a treatment are evaluated.

Through the implementation of its HTA pilot, Japan's MHLW has taken an important first step in developing a scientifically based system that can inform the optimal use of its limited resources. As Japan and other countries establish new HTA processes, support from global experts in HTA will be valuable to ensure that lessons learned from other countries can be leveraged and operationalized.

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Additional information

To learn more about ISPOR's health technology assessment Special Interest Group, go to https://www.ispor.org/sigs/HTA.asp.

Q&A

Real-World Evidence and Health Technology Assessment: An Interview with Dennis Raisch, PhD

Value & Outcomes Spotlight had an opportunity to talk with Dennis Raisch, PhD, Professor, University New Mexico College of Pharmacy, Albuquerque, NM, USA. Dr. Raisch served as ISPOR Chair of the Risk Benefit Special Interest Group from 2004 to 2012 and as Chairman of the Student Chapter Faculty Advisory Council 2015-7.

Dr. Raisch's interests include research regarding the effectiveness, safety, public policies, and adoption of biosimilars, and the identification of rare, serious adverse events associated with pharmaceuticals, including biologicals.

Value & Outcomes Spotlight: **Why do you think there is substantial variability in the uptake of biosimilars across different countries?**

Dennis Raisch: There are several reasons. First, the FDA was slower in providing regulations for biosimilars compared to Europe. The regulatory pathway was not finalized in the United States until 2015 compared with 2005 by the European Medicines Agency (EMA). The first biosimilar was approved by the EMA in 2006 compared to 2015 in the United States. Second, patent litigation occurs more frequently in the United States and results in marketing delays and added costs. For example, although the first United States biosimilar (filgrastim-sndz) was approved in March 2015 it was not marketed until November 2015. The patent litigation process can be very costly and significantly delay market access. Third, most state boards of pharmacy regulations regarding interchangeability of biosimilars require that the FDA specify that the product is interchangeable. The FDA has not designated any of the approved biosimilar products as interchangeable.[1] Fourth, as with generics, there is resistance from patients regarding use of biosimilars, especially if they have already begun treatment with the reference product. Many state board of pharmacy regulations include requirements for patient acknowledgement that a biosimilar is being used. Unless biosimilars provide significant cost savings for the payer and the patient (regarding their co-pay), the incentives to use biosimilars is insufficient.

What steps should the scientific community be doing to ensure post-approval studies of biosimilars are generating valid evidence?
The most important step will be assessment of effectiveness and safety. Although post-approval studies might be accomplished with large database analyses, it may take several years to acquire sufficient numbers of patients to identify differences. In addition, the details required to accurately specify differences is unlikely to be captured in administrative databases. Studies using patient registries would be ideal to address these concerns. Post-approval randomized, controlled clinical trials (RCTs) could be implemented, but these studies are very costly and unlikely to be large enough or long enough to identify differences in safety. Pragmatic trials with sufficient methods to address bias and confounding will be helpful. Cost effectiveness analyses, systematic reviews, and meta-analyses will be needed. Regarding safety, other types of active pharmacovigilance with specific data collection tools might be feasible in some situations.

What are the biggest challenges in conducting post-approval studies of biosimilars?

Patient registries, RCTs, and active pharmacovigilance studies can be very costly and results may not be available for many years. Furthermore, until uptake of biosimilars increases, it will be difficult to conduct post-approval studies. Specifically, large numbers of patients exposed to biosimilars are needed to make valid comparisons to reference products in post-approval studies. For example, pharmacovigilance research for a safety concern occurring in 1 in 1000 patients would require at least 3000 patients exposed to the biosimilar. Implementing methods to address bias and confounding in observational studies can increase those sample size requirements substantially.

What evidence do stakeholders (physicians, payers, patients) need to accept biosimilars once they are approved, particularly for indications that received approval through extrapolation?

Education is a key requirement to stimulate uptake of biosimilars. Among patients and even prescribers, there is limited awareness or understanding of biosimilars. Given baseline understanding, post-approval research of safety and effectiveness is needed. This applies for all indications, including those approved through extrapolation.

Do you anticipate any difference in uptake of the monoclonal antibodies for the oncology indications than what we have seen with the uptake of anti-TNFs?

The psychological impact of life or death associated with oncologic indications further limit the willingness of patients and providers to use biosimilars.

If you had a magic ball to see into the future, what will the global biosimilar market look like 10 years from now?

Globally, biosimilar utilization will continue to grow and eventually biosimilars will be prescribed in a similar manner as generics and considered equivalent in safety and effectiveness as reference products. That scenario will lead to price reductions of reference products. Another response by pharmaceutical companies will be to continue to develop new biologicals, as well as to improve and modify reference biologicals (ie, biobetters). The uptake of biosimilars in the United States will continue to lag, unless a more efficient and centralized healthcare system is adopted.

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