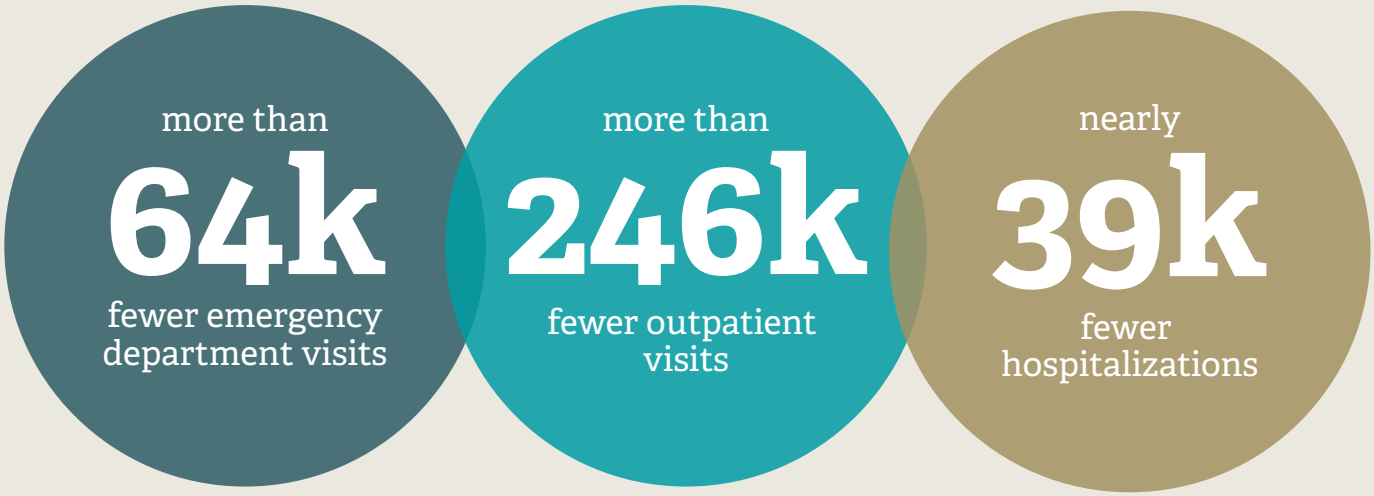
ANALYSIS GROUP ECONOMIC, FINANCIAL and STRATEGY CONSULTANTS

HEALTH CARE BULLETIN

Winter 2018

Analysis Group modeling indicates that, over a five-year period, using abuse-deterrent opioids for a single prescription opioid – morphine – could result in:



SOURCE: "A HARM REDUCTION MODEL TO QUANTIFY POTENTIAL MISUSE/ABUSE REDUCTION AND ABUSE-RELATED EVENTS AVOIDED FROM ABUSE DETERRENT OPIOIDS," ALAN WHITE, TIM SPITTLE, GWENDOLYN NIEBLER, JEFFREY DAYNO, COLVILLE BROWN, AND NATHANIEL KATZ, PRESENTED AT PAINWEEK 2017, SEPTEMBER 7, 2017.

The Opioid Epidemic: Analysis Group's Work in Tracking Impacts and Developing Responses

Abuse and misuse of opioids has reached "epidemic" proportions, according to numerous news reports, the U.S. Department of Health and Human Services, the Centers for Disease Control, and the White House. Misuse of prescription opioids, such as oxycodone, hydrocodone, morphine, and methadone, has become a major focus of regulators, manufacturers, prescribers, and researchers. This issue of our Health Care Bulletin *highlights some of the areas in which we believe our work is helping to make a difference: developing* ***Suspicious Order Monitoring*** *programs and tracking the impact of* ***abuse-deterrent opioids*** *– including the* ***economic costs of abuse****.*

Also inside:

Making the Right Call: SOM for Prescription Opioids

As the opioid crisis continues, the Suspicious Order Monitoring (SOM) requirement has become an increasingly important enforcement tool for the U.S. Drug Enforcement Agency (DEA).

CRYSTAL PIKE,
MANAGING PRINCIPAL

KENNETH WEINSTEIN,
VICE PRESIDENT

NICHOLAS VAN NIEL,
ASSOCIATE

ADAPTED FROM "A NEW STANDARD FOR SUSPICIOUS ORDER MONITORING: PART 1," BY CRYSTAL PIKE, KENNETH WEINSTEIN, AND NICHOLAS VAN NIEL, PUBLISHED ON LAW360.COM, AUGUST 21, 2017.

This regulatory clause, which dates back to changes to the 1970 Controlled Substances Act (CSA) enacted in 1971, requires any DEA-registered entity distributing opioids or other controlled substances to "design and operate a system to disclose ... suspicious orders of controlled substances." Suspicious orders are defined as "orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency."

However, the DEA has provided little guidance beyond these words in the nearly 50 years since the clause's enactment. Most recently, the DEA's position in cases involving wholesale distributors reveals that the agency has set a high bar for monitoring orders of controlled substances – particularly in terms of making use of available data. In the D.C. Court of Appeals ruling involving Masters Pharmaceutical in early 2017, for example, the court found that the DEA was within its rights to revoke Masters' controlled substance license due to failures to comply with the SOM requirement. Like many pharmaceutical distributors, Masters employed a statistical algorithm to make an initial screen of pharmacy orders. Masters then selected a subset of the orders flagged by the algorithm and subjected them to manual review. Following the manual review, Masters would report suspicious orders to the DEA.

One of the key points of contention in the case was whether Masters' algorithm and review process appropriately used all available data and analytics to determine which orders to report. Although the SOM statute defines suspicious orders in terms of size, pattern, and frequency, the Masters decision emphasizes that these are not an exhaustive list of criteria. Other red flags include, for example, the relative volumes of controlled and non-controlled substances, as well as mismatches between ordering and actual dispensing at the pharmacy. However, data on dispensing are not generally available to distributors in the regular course of business.

The DEA administrator's original decision in Masters states that "a distributor is required to use the most accurate information available." What constitutes availability, however, is not straightforward and gives rise to questions about the DEA's application of the standard.

In some cases, Masters' manual review process for orders flagged by the algorithm involved obtaining additional pharmacy utilization data to assess the proportion of prescriptions attributable to controlled substances. However, in other instances, additional data of this type were not obtained. According to the court, this selective approach was inadequate in analyzing additional data beyond size, pattern, and frequency.

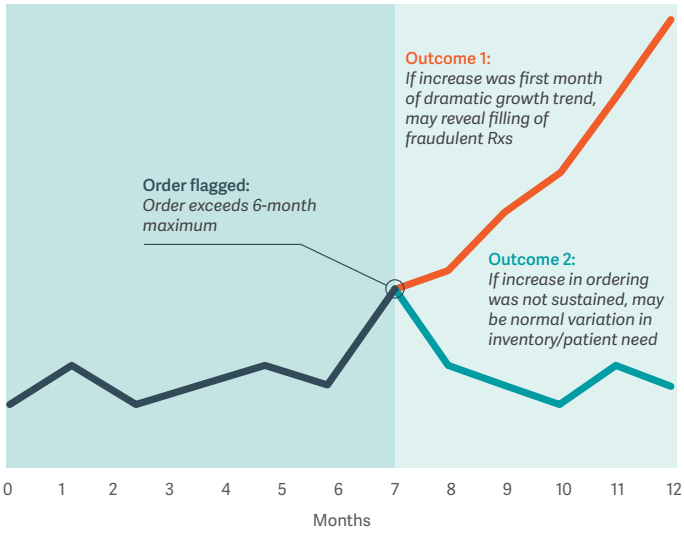
Accuracy Is Critical, but Involves Important Tradeoffs

The court underscores the perception that the bar to dispel the possibility of suspicion for a flagged order is high. While Masters viewed the orders initially flagged only as potentially suspicious, the decision rejects this approach, indicating that any orders flagged by an algorithm should be considered suspicious unless otherwise dispelled. Given the derivative requirements to

block and report suspicious orders, there is a gulf between "potentially suspicious" and "suspicious" that may be as wide as that between "innocent until proven guilty" (or arrested and awaiting trial) and "guilty until proven innocent" (or convicted, pending appeal).

The costs of misclassifying orders are high, whether a distributor is blocking legitimate orders meeting patient needs or is fulfilling orders to pharmacies later found to have illegitimate activity. However, no algorithm or review process is guaranteed to distinguish legitimate from illegitimate activity; some improper dispensing can only be identified with certainty based on hindsight. For example, the figure below shows how an order initially may be flagged by a statistical algorithm based on a customer's prior history, and only with the benefit of hindsight does the presence or absence of illegitimate dispensing become clear.

Hypothetical Review of Order Flagged by Algorithm as Suspicious



While it may be possible to calibrate a statistical approach based on analysis of pharmacies known to have had illegitimate dispensing in the past, data on such pharmacies are often limited. Moreover, there is no *ex ante* guarantee that such an approach will reliably identify the next issue, nor that the resulting algorithm will appropriately filter out legitimate activity. Thus, pharmaceutical distributors must operate with incomplete information, as certain types of data may never be available until well after the fact.

Nonetheless, given the high cost of imprecision, distributors should strive to make the best use of the data that are available to them, keeping up with current trends to avoid an overly

Continued on p. 4

Features

Making the Right Call: SOM for Prescription Opioids, Continued from p. 3

backward-looking approach. They should also carefully consider the balance between sensitivity and specificity.

A highly sensitive algorithm will cast a wide net and will be unlikely to miss any genuinely suspicious activity, but it will also flag many orders that are not unusual. With an overly sensitive system, a distributor that blocks and reports all orders could easily put legitimate patient needs in jeopardy. Because human reviewers may become ineffective if they are reviewing a large number of orders that were flagged unnecessarily, a distributor may decide that it is safer not to rely on manual review at all and end up over-reporting suspicious orders to the authorities, which does not advance the cause.

Conversely, a highly specific algorithm will have a larger share of its flagged orders that prove to be of genuine concern, but may miss others. In this scenario, review of flagged orders will be more efficient than with an overly sensitive system. But that could also come at a high cost, as some illegitimate orders may not be identified.

Maintain Consistency, but Make Improvements

The Masters decision stresses the importance of consistency in the review process. Absent explicit regulatory guidance on the SOM requirement, internal consistency may act as the most straightforward standard. The decision found that Masters' review process was inconsistent across orders and conflicted with the approach laid out in its own compliance documentation.

At one extreme, Masters could simply have blocked and reported every order flagged by its algorithm. However, this approach would certainly have blocked many legitimate orders. Consistency requires ongoing efforts to monitor the review process and regularly obtain additional data. Setting up standard reports with key data analytics pertaining to flagged orders can make the manual review process more systematic and less *ad hoc*. Maintaining consistency may also require periodic modifications to the statistical algorithm to incorporate analyses that are repeatedly identified as part of manual review.

Distributors who are not inclined to incorporate manual review into their SOM may still want to minimize risk by setting up efficient statistical tools tailored to their customer base to comply with the Effective Controls Against Diversion requirement.

With SOM being featured as a critical plank in the DEA's approach to countering the opioid crisis, distributors will need to make increased efforts to meet these requirements. Limited guidance, the lack of sufficient data for calibration, and incomplete customer information present real challenges. Even with carefully thought-through statistics and well-trained reviewers, the decision of whether to report an individual order is difficult to systematize. The principles discussed above can help inform those decisions by providing a sound combination of statistics and judgment. ■

Abuse-Deterrent Opioids and the Economic Costs of Abuse

How can industry participants help curb opioid abuse while maintaining appropriate access to care for patients?

NOAM Y. KIRSON,
VICE PRESIDENT

HOWARD G. BIRNBAUM,
PRINCIPAL

ALAN G. WHITE,
MANAGING PRINCIPAL

Prescription opioid medications can be effective for patients suffering from painful conditions. At the same time, prescription opioid abuse – including dependence, overdose, and poisoning – has become a national public health concern.

Beyond the human toll of the increasing number of deaths traceable to abuse, prescription opioid abuse comes with considerable economic burden. Analysis Group's research shows that prescription opioid abuse is associated with sharp increases in health care costs and medical resource utilization,

as well as with higher caregiver burden, substantial workplace costs (lost earnings, medically related absenteeism, and disability claims), and criminal justice costs.

Recently, we examined the excess health care costs of opioid abuse – that is, costs documented for diagnosed abusers, beyond those found for a similar control group of patients who were not diagnosed as abusers. (See figure.) Excess costs begin accumulating well before the abuse diagnosis, spike during the incident diagnosis month, and remain elevated for 18 months following diagnosis. Prior to and including the diagnosis, a larger proportion of excess costs is incurred by use of emergency departments and inpatient services, perhaps indicating that acute abuse-related events lead to formal abuse diagnoses. Following diagnosis, maintenance care costs (outpatient services and rehabilitation facilities) tend to be higher, suggesting that diagnosed abusers continue to receive treatment in less-intensive forms.

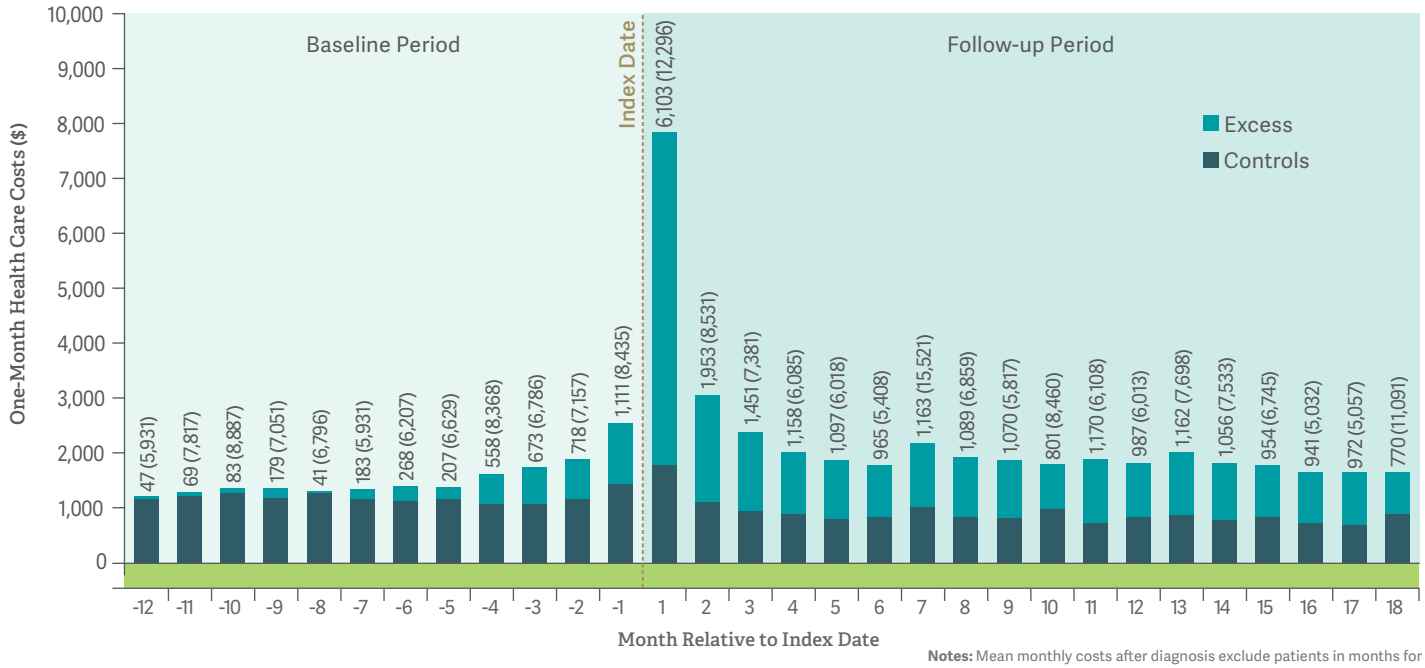
Policy interventions such as Suspicious Order Monitoring programs are intended to help identify potential abuse earlier. Additionally, some pharmaceutical manufacturers have developed abuse-deterrent opioids (ADOs) – that is, opioids with properties intended to reduce the risk of abuse. The U.S. Food and Drug Administration (FDA) has approved a number of these in the past several years.

Recent results from our work suggest that ADOs may indeed hold the potential to reduce real-world abuse and total costs to the health care system. However, our studies have also raised the possibility that some patients may avoid treatment with ADOs when they become available, and that those who do are more likely to be abusers. This may be an unintended consequence of introducing ADOs in a therapeutic landscape that still includes both opioids without abuse-deterrent properties and illicit substances such as heroin.

These findings suggest that ADOs are part of a larger set of policy tools and should be considered along with additional initiatives, such as greater education of physicians, increased access to substance use treatment, and more rigorous identification and monitoring to identify patients at high risk of abuse. ■

SOURCES: "USE OF PRESCRIPTION OPIOIDS WITH ABUSE-DETERRENT TECHNOLOGY TO ADDRESS OPIOID ABUSE," EDWARD MICHNA, NOAM Y. KIRSON, AMIE SHEI, HOWARD G. BIRNBAUM, RAMI BEN-JOSEPH, *CURRENT MEDICAL RESEARCH AND OPINION*, 30:8, 1589-1598 (2014); "DRIVERS OF EXCESS COSTS OF OPIOID ABUSE AMONG A COMMERCIALLY INSURED POPULATION," LAUREN M. SCARPATI, NOAM Y. KIRSON, MIRIAM L. ZICHLIN, ZITONG B. JIA, HOWARD G. BIRNBAUM, JAREN C. HOWARD, *AMERICAN JOURNAL OF MANAGED CARE*, MAY 22, 2017; "OPIOID ABUSE: A DETAILED EXAMINATION OF COST DRIVERS OVER A 24-MONTH FOLLOW-UP PERIOD," LAUREN M. SCARPATI, NOAM Y. KIRSON, ZITONG B. JIA, JODY WEN, JAREN HOWARD, *JOURNAL OF MANAGED CARE & SPECIALTY PHARMACY*, JUNE 6, 2017; "A HARM REDUCTION MODEL TO QUANTIFY POTENTIAL MISUSE/ABUSE REDUCTION AND ABUSE-RELATED EVENTS AVOIDED FROM ABUSE DETERRENT OPIOIDS," ALAN WHITE, TIM SPITTLE, GWENDOLYN NIEBLER, JEFFREY DAYNO, COLVILLE BROWN, NATHANIEL KATZ, PRESENTED AT PAINWEEK 2017, SEPTEMBER 7, 2017.

Mean Per-Patient-Per-Month Excess Health Care Costs During the 30-Month Study Period



Notes: Mean monthly costs after diagnosis exclude patients in months for which they no longer have continuous eligibility. Standard deviations are shown in parentheses.

Why Biosimilar Introduction May Be Different

Biologic drugs comprised seven of the ten highest-revenue drugs worldwide in 2016. Pharmaceutical companies are developing biosimilar versions of these lucrative products, and to date seven biosimilars have been approved by the U.S. Food and Drug Administration (FDA) for five biologic drugs. However, while biosimilars are the biologic drug corollary to generic drugs, they have important differences from traditional generics.

Biosimilars and their branded biologic counterparts are complex, organism-based medications that are "grown" rather than chemically manufactured. This leads to more complexity and variability in production processes and in the biosimilar products themselves. These circumstances, in turn, create a cascade of impacts throughout the distribution chain, affecting everything from production costs and marketing strategies, to regulatory oversight of efficacy and competition, to physician uptake, to pharmacy fulfillment and payer reimbursement considerations.

Understanding the chain of impacts is critical to understanding the economic implications of biosimilar competition and the unique issues raised in prospective intellectual property, antitrust, product liability, and other litigation. ■

PBMs and Health Insurers

- Customized rebating strategies for both brand biologic and biosimilar manufacturers
- Emphasis on efficacy and safety findings for individual biosimilar products, due to variability from reference biologic

Pharmacies

- Modest influence of automatic substitution, as few biosimilars may receive an interchangeability rating due to scientific challenges, uncertainty, and regulatory costs

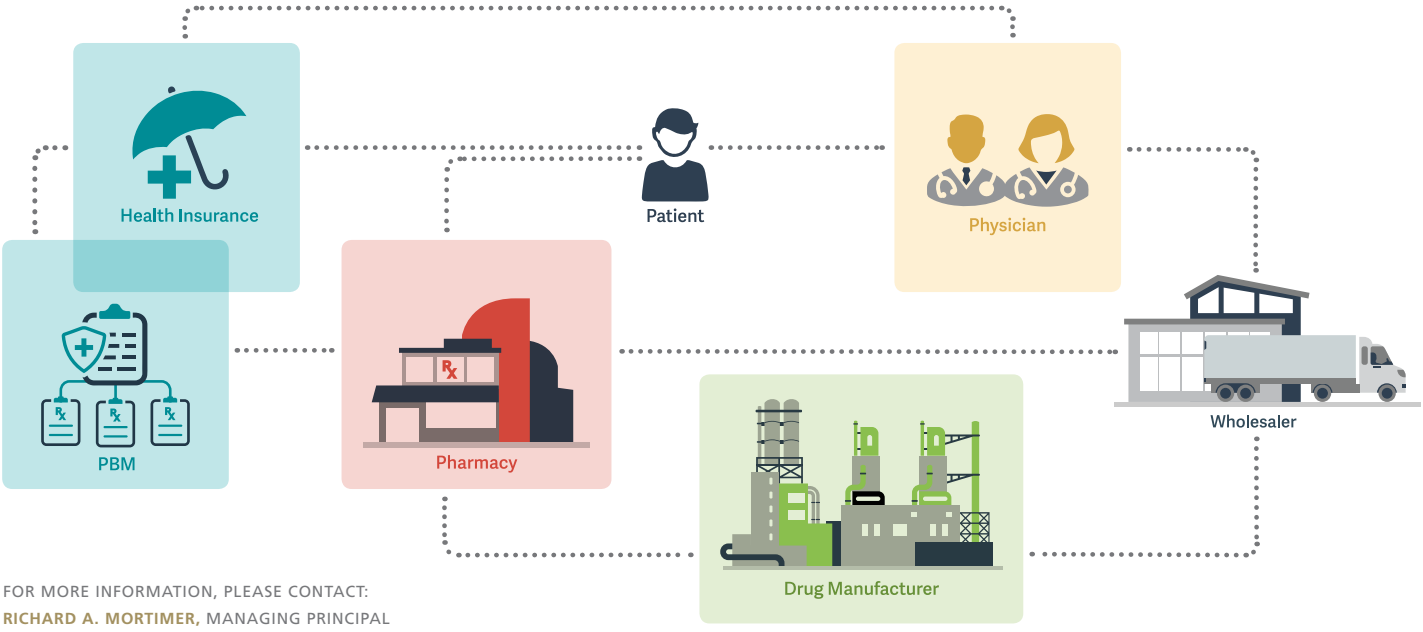
Drug Manufacturers

- Marketing of biosimilars and promotion of individual characteristics rather than a generic strategy of pure price competition
- Vertical contracting and rebating with pharmacy benefit managers (PBMs) and others for preferred access
- Post-marketing trials on safety and efficacy to increase physician uptake

Physicians

- Need for additional real-world evidence on efficacy and safety of individual biosimilars, and importance of individual physician experience
- Reimbursement considerations due to "buy and bill" nature of many physician-administered biologics

Impacts Across the Biosimilar Distribution Chain



FOR MORE INFORMATION, PLEASE CONTACT:
RICHARD A. MORTIMER, MANAGING PRINCIPAL

Causation in Product Liability: Taking a New Look

Proof of general causation can be an important precursor to establishing specific causation.

MEI SHENG DUH,
MANAGING PRINCIPAL

BRIAN ELLMAN,
VICE PRESIDENT

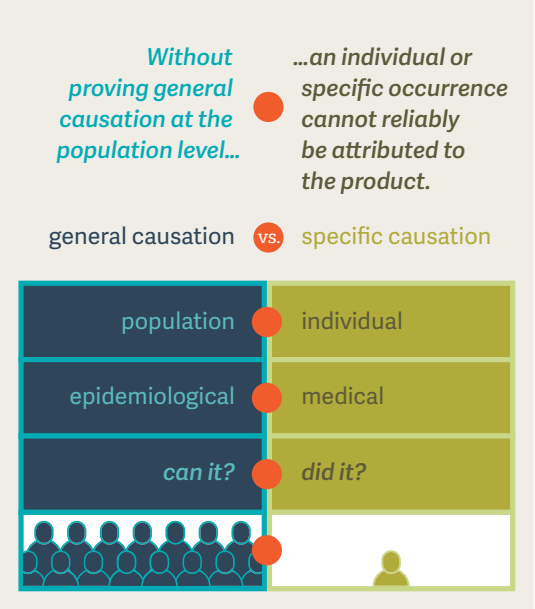
Product liability litigation for pharmaceuticals and medical devices often relies on physician testimony to establish causality for a plaintiff. In such cases, plaintiffs, defendants, jurists, and jurors alike focus on the question, "Did the drug (or device) cause a particular side effect for this person?" However, as Analysis Group Managing Principal Mei Sheng Duh points out, inferring a definite causal relationship based on any individual patient experience is unlikely to pass basic thresholds of scientific reliability.

Dr. Duh suggests that the causal relationship between a drug and an observed adverse event should be assessed at two different levels: (1) general and (2) specific. (See figure.) First, epidemiologists can test the association between a drug and a particular adverse event at the population level. This is often referred to as "general causation." Following that, physicians may look at a particular patient's medical history to determine whether an adverse event in that single individual is causally related to the use of the drug. This is often referred to as "specific causation."

As Dr. Duh explains, at the population level, the aim of causality assessment is to answer the question, "Can it?" – that is, is it possible that the given drug could cause a particular adverse event in anyone? At the individual level, however, causality assessment answers the question, "Did it?" – did the drug given to a particular individual cause the particular adverse event? The first question is the realm of the epidemiologist, while the second is the realm of the physician.

For example, in a recent product liability matter, a team from Analysis Group led by Dr. Duh, Vice President Brian Ellman, and Analysis Group affiliate Professor Lee-Jen Wei, of Harvard University's Department of Biostatistics, used a population-level approach to show that, in general, exposure to the at-issue product did not increase the risk of cardiopulmonary arrest while undergoing hemodialysis, as was alleged. Instead, they showed that other factors were likely to explain such events.

Without first answering the "can it" question, answering the "did it" question could lead to the fallacy that an idiosyncratic association based on one individual is indicative of a causal relationship. Hence, litigators should not lose sight of the foundational importance of the "Can it?" question in product liability lawsuits. ■



Patient-Reported Outcomes: Emerging Developments and Innovative Approaches

Analysis Group led a symposium on patient-reported outcomes (PROs) at the ISPOR 22nd Annual International Meeting.

Many assessment criteria are used by the U.S. Food and Drug Administration (FDA) to help determine the efficacy and safety of a pharmaceutical product. One area that is receiving increased attention from stakeholders across the health care industry relates to PROs, a core set of measures for clinical outcome assessments (COAs) valued by the FDA to support patient-focused care.[1] PROs can assess whether a drug provides benefits by measuring the impact of the treatment on a patient's symptoms, mental state, or function. Treatment benefits captured by valid PRO measures have been used to support medical product labeling claims approved by the FDA and/or the European Medicines Agency. As an extension of PROs, the health utilities generated from PRO measures are a critical component for informing decision making in the context of a Health Technology Assessment (HTA), a systematic evaluation of the properties, effects, and impacts of health technologies (i.e., medical interventions).

Given the rising importance of health economic and outcomes evaluations of medical interventions, the need for short, valid, sensitive, and reproducible PRO tools to capture the benefits of treatments has never been greater. During a symposium at the ISPOR 22nd Annual International Meeting, Managing Principal Eric Wu discussed new developments in PROs and HTAs with two leading academics in the field: John E. Ware, professor and chief of outcomes measurement science in the Department of Quantitative Health Sciences at the University of Massachusetts Medical School, and an Analysis Group affiliate; and John E. Brazier, professor of health economics and dean of the School of Health and Related Research at The University of Sheffield, U.K. Both are internationally recognized leaders who have established expertise in developing, standardizing, and applying health metrics to assess PROs. The topics discussed during the symposium addressed the growing need for reliable, valid, and responsive health measurement tools that can be readily integrated into the planning and design phase of clinical trials and HTA submissions. Analysis Group Managing Principal Mei Sheng Duh moderated the symposium.

The aging population and rising prevalence of chronic conditions around the world are creating demand for ways to quantify not only patient health, but also other benefits that a patient receives (e.g., dignity, autonomy, sense of belonging). Such measurement tools will lead to better, more accurate, and more sensitive empirical data; will support the claim of a medical product being safe and efficacious; and will provide meaningful benefits to patients for improved health-related quality of life (HRQL).

Professor Ware discussed the foundation of conceptualizing and quantifying HRQL, and emphasized the essential domains of health along with the advances in the standardization of disease-specific PRO measures across health conditions. Professor Brazier then described parallel developments in the utility field, such as condition-specific preference-based measures and how they compare to generic utility measures; extending generic

ERIC WU,
MANAGING PRINCIPAL

JOHN E. WARE,
PROFESSOR, UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL

JOHN E. BRAZIER,
PROFESSOR OF HEALTH ECONOMICS, THE UNIVERSITY OF SHEFFIELD, U.K.

MEI SHENG DUH,
MANAGING PRINCIPAL

utility measures to incorporate higher levels of functional health and well-being; and calibrating different measures through linking and mapping. Dr. Wu shared the common challenges encountered in outcomes evaluation in the context of HTAs and discussed the practical approaches for utility generation, including new developments in utility estimation to support HTA submissions.

During his remarks, Dr. Wu noted that HTA agencies generally recommend using utility values directly from clinical trials. However, this is not always available or feasible. Some common challenges include insensitive utility measures, lack of information due to rarity of a disease, underestimation of utility impacts because of the nature of disease progression, and limited duration of a clinical trial. Therefore, careful and strategic considerations should be given for utility assessment during clinical trial planning. Several case studies presented by Dr. Wu addressed the potential approaches to apply for different scenarios in HTA submissions.

As the symposium participants discussed, the recent advances in psychometric and utility methods appear to be increasingly gaining adoption, which will continue to help alleviate patient burden and introduce greater efficiencies. These are critical aspects when it comes to demonstrating product value in health economic and outcomes evaluations. ■

1 SEE: HTTPS://WWW.FDA.GOV/DRUGS/DEVELOPMENTAPPROVALPROCESS/DRUGDEVELOPMENTTOOLSQUALIFICATIONPROGRAM/UCM284077.HTM.

Using PROs to Identify Quality of Life and Work Productivity Benefits of Adalimumab Use

A recent study related to patient-reported outcomes (PROs) on adalimumab (Humira), an immunosuppressive medication, found that the medication enhances quality of life and work productivity in patients with moderate to severe hidradenitis suppurativa (HS). Analysis Group undertook this study in collaboration with AbbVie (manufacturer of Humira) and Dr. Alexandra Kimball, professor at Harvard Medical School and president and CEO of Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center.

The study, "Health-related quality of life and work productivity associated with HiSCR and NRS30 response among patients with moderate to severe hidradenitis suppurativa," was authored by Dr. Kimball, Analysis Group Managers Min Yang and Yan Song, and Wendell Valdecantos and Arijit Ganguli of AbbVie. Its findings were presented at this year's American Academy of Dermatology Annual Meeting in March, and an abstract of the study was published in the *Journal of the American Academy of Dermatology* in June.

The study combined data from two phase 3 clinical trials in which 455 patients were either administered adalimumab therapy or a placebo. Focused on two indicators – NRS30, a measurement of pain control, and Hidradenitis Suppurativa Clinical Response (HiSCR), a measurement of HS lesion control – the study found that both objective disease control and skin-pain control are associated with improved quality of life and work productivity in patients with HS. In addition, patients who had good disease control and who achieved skin-pain control reported additional benefits in PROs.

The Analysis Group team had previously worked with Dr. Kimball and AbbVie to assess the validity, responsiveness, and meaningfulness of HiSCR as the clinical endpoint for HS treatment, using phase 2 data. The findings of that study, which played a pivotal role in obtaining FDA approval, were published in the *British Journal of Dermatology*, with Dr. Kimball once again the lead author. ■

Biopharma Value-Based Pricing: How to Make It Work?

Value-based pricing/contracts (VBCs) have emerged as a way for biopharmaceutical companies and payers to demonstrate how to deliver better health care, while reducing costs and financial risks.

CHRISTIAN FROIS,
VICE PRESIDENT

ERIC WU,
MANAGING PRINCIPAL

FOR MORE INFORMATION, SEE "OUTCOMES-BASED CONTRACTING EXPERIENCE: RESEARCH FINDINGS FROM U.S. AND EUROPEAN STAKEHOLDERS," BY A TEAM OF RESEARCHERS INCLUDING CHRISTIAN FROIS AND ERIC WU, PUBLISHED IN *JOURNAL OF MANAGED CARE & SPECIALTY PHARMACY*, OCTOBER 2017.

Pressure is mounting in the United States and Europe to decrease overall health care spending and increase stakeholder accountability. For example, the U.S. Department of Health and Human Services aims to tie 90% of Medicare payments to value by 2018. VBC schemes are also common in Italy, Germany, and Spain, and gaining popularity in France and the U.K.

In this context, outcomes-based contracts (OBCs) are leading the charge. OBCs are most often confidential agreements that tie price to specified patient outcomes. OBCs can be complex; still, OBCs have been used in many recent high-profile biopharmaceutical product launches, including therapies related to hepatitis, high cholesterol, heart failure, and even oncology.

A recent study, led by Analysis Group and funded by Novartis Pharmaceuticals, is the first to characterize historical OBC activity and trends in the U.S. and EU-5 (France, Germany, Italy, Spain, and the U.K.) – going beyond the limited information provided by companies' publicized activity. The research revealed that the level of OBC activity was previously underestimated, and that the U.S. and EU-5 can expect OBC activity to nearly double in the next five years. (See figure.)

Making It Work

From our work supporting the exploration and implementation of VBCs, and OBCs in particular, we can identify several key success factors. First, it is important to recognize that not all payers are the same, in either the U.S. or Europe. To develop a successful VBC, manufacturers must identify each target payer's motivation. By aligning the contract's key features with the core rationale for using or not using the product, the benefits become clear to both sides.

Second, we have found that it is best to keep the process as simple as possible. The complexity of designing and implementing a VBC is one of the main hurdles for both manufacturers and payers, so it is helpful to work with an experienced third-party team that can advise on how to keep complexity at bay, while keeping the focus on the value of the product and the deal for both parties. The team should help define and measure the right outcomes with the most relevant data, advise on manufacturer-payer commercial negotiations, and address legal considerations (e.g., anti-kickback statutes, off-label promotion, Medicaid best price).

Thinking through these issues prior to reaching out to payers is often the key to the successful use of VBCs. ■

Number of OBCs per Payer Interviewed

Country	Past 5 Years	Next 5 Years
USA	~3 (0–4 range)	~7–8 (1–20 range)
ITA	~50	60–70
SPA	5–8	~50
GER	~20	40
UK	5–6	20–40
FRA	5	10

Source: Analysis Group interviews.

Spotlight on Europe

Analysis Group's global health care team contributes to pharmaceutical manufacturers' product strategies and decision making of major regulatory and health technology assessment (HTA) agencies, payers, physicians, and patients.

Drawing on resources from our offices across North America, Europe, and Asia, including in London, Brussels, and Paris, we provide specialized expertise in health economics and outcomes research (HEOR), epidemiology, market access strategies, pricing, and reimbursement.

In Europe, our experience includes:

- Indirect treatment comparisons to generate comparative-effectiveness evidence and support HTA submissions
- Developing cost-effectiveness models and budget impact models for HTA submissions
- Developing global value dossiers to support launch in multiple countries
- Generating real-world evidence (RWE) using multi-country chart reviews and database analyses
- Developing and validating new patient-reported outcome (PRO) measures and application of PROs in multi-country patient surveys
- Analyzing clinical trial data to support PRO labels
- Conducting safety studies and submitting evidence to regulatory agencies
- Providing market access strategies through market research and collecting insights from payers and providers through advisory board and in-depth interviews

Some examples of our recent European work are highlighted below.

- We developed cost-effectiveness models that resulted in positive recommendations from the National Institute for Health and Care Excellence (NICE) for the treatment of hidradenitis suppurativa and of non-small cell lung cancer (NSCLC).
- The post-authorization safety study we conducted for an antifungal drug led to favorable reviews of our client's post-marketing programs by both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA).
- At European ISPOR 2017, we organized and presented a symposium on "Evaluating survival benefits in technology appraisals of innovative oncology drugs," in collaboration with Dr. Nicholas Latimer from The University of Sheffield.
- Working with a major global pharmaceutical company, we analyzed historical activity in outcomes-based contracting, comparing trends in the United States and the EU-5 (France, Germany, Italy, Spain, and the United Kingdom). ■

A New Landscape for Comparative Effectiveness Research

There is a clear movement toward a more pragmatic application of real-world data to meet the needs of both regulators and payers.

DAVE NELLESEN,
VICE PRESIDENT

HOWARD G. BIRNBAUM,
PRINCIPAL

PAUL E. GREENBERG,
MANAGING PRINCIPAL

ADAPTED FROM "PERSPECTIVES ON DECISION MAKING IN A WORLD OF COMPARATIVE EFFECTIVENESS RESEARCH," BY DAVE NELLESEN, HOWARD G. BIRNBAUM, AND PAUL E. GREENBERG, IN *DECISION MAKING IN A WORLD OF COMPARATIVE EFFECTIVENESS RESEARCH*, EDITED BY HOWARD G. BIRNBAUM AND PAUL E. GREENBERG, SPRINGER NATURE SINGAPORE PTE LTD., 2017.

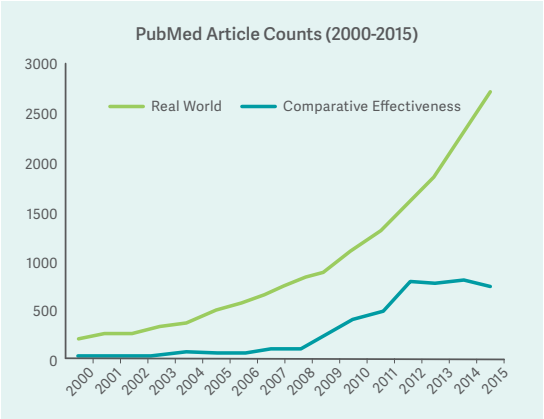
Over the past decade, there have been signs that the landscape for comparative effectiveness research (CER) is shifting. When the idea of CER – that is, evidence on the effectiveness and consequences of different treatment options that would inform decision making – was conceived nearly a decade ago, it was framed in a context where the availability of real-world data and methods for analysis were relatively limited. Accordingly, clinical trials played a necessary and central role in assessing comparative effectiveness.

However, the number of clear-cut success stories for large, centralized comparative clinical trials has been modest, especially considering the vast number of treatment and resource allocation decisions where evidence is needed. Such trials are also costly to undertake, and necessarily only include a limited population.

By contrast, use of observational studies to provide evidence of comparative effectiveness has benefited from the growing availability of data from a wide range of sources, such as electronic health records, medical chart reviews, administrative data, and surveys. Such data can often be gathered more quickly and at a lower cost than in clinical trials; in addition, the use of more widely accessible, real-world populations can make the results more generalizable. Finally, new approaches to data analysis, such as the use of machine learning, may help overcome historical limitations of CER, wherein a well-designed clinical study may find no benefit on average while a specific subset of patients might still gain from the treatment.

For these and other reasons, in some situations observational data may be a better fit for decision makers as part of efforts to contain costs and maximize value for money spent. An analysis of recent literature in PubMed indicates that interest in real-world studies continues to rise while the number of CER studies has leveled off (see figure), which parallels a similar plateau seen for CER clinical trials (data not shown).

An equilibrium can likely be found that balances both approaches. Nevertheless, as the availability and interconnectedness of real-world data increase, comparisons of clinical and cost effectiveness using real-world data are likely to become the standard, with growing influence on the commercial success of new health technologies. ■



Source: Analysis Group research. The NCBI PubMed database was searched using the terms "real world" and "comparative effectiveness" in title and abstract fields on 9/16/2016.

Making More Precise Health Care Decisions with Machine Learning

The health care industry, with its great variety and richness of data sources, is a natural area for application of machine learning algorithms in comparative effectiveness research (CER).

Especially within the context of CER in health care, machine learning algorithms are being used to improve productivity, evaluate alternative interventions, and develop new treatments. They often are used to discover intricate relationships between inputs and outputs that are hard to anticipate in advance. They are therefore particularly well suited for predictive tasks, such as predicting the future onset or progression of a disease, or the treatment to which an individual is most likely to respond.

Precision medicine relies on such tools to support joint decision making by patients and their providers regarding the best treatment plan given the patient's individual characteristics, including lifestyle, environment, and genetics. The size and complexity of the health data required are daunting, as precision medicine ideally relies on information from all available sources, including electronic health record systems, patient-reported data, and genomic data. The potential upside from being able to use all these data for developing a treatment plan can be game changing, or even life saving.

Machine learning algorithms can also support the creation and revision of treatment guidelines, providing a deeper understanding of which genetic markers are associated with which side effects, for example, or how patients who followed the treatment guidelines fared relative to those who did not. These new approaches to data analysis may also help provide insight where treatment effects are heterogeneous, allowing researchers and practitioners to identify specific subsets of patients who might benefit from a treatment even when no benefit is discernible on average. ■

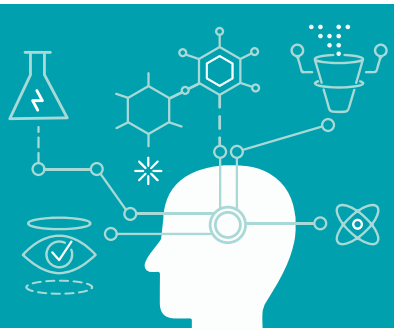
LISA PINHEIRO,
MANAGING PRINCIPAL

JIMMY ROYER,
VICE PRESIDENT

NICK DADSON,
ASSOCIATE

ADAPTED FROM "DECISION MAKING WITH MACHINE LEARNING IN OUR MODERN, DATA-RICH HEALTH-CARE INDUSTRY," BY NICK DADSON, LISA PINHEIRO, AND JIMMY ROYER, IN *DECISION MAKING IN A WORLD OF COMPARATIVE EFFECTIVENESS RESEARCH*, EDITED BY HOWARD G. BIRNBAUM AND PAUL E. GREENBERG, SPRINGER NATURE SINGAPORE PTE LTD., 2017.

> "The potential upside [for machine learning] can be game changing, or even life saving."



Book Review

Lou Garrison (president of ISPOR) recently reviewed Analysis Group's CER book, calling it "…a much-needed addition to our field … valuable insights on how CER is or can be used." **Visit analysisgroup.com/CER to read the full review.**

Planting Trees to Reduce Health-Related Costs

Recent research conducted by Analysis Group found that increased tree planting could benefit millions of people who are adversely affected by particulate matter (PM) pollution, while reducing health-related costs.

HOWARD G. BIRNBAUM,
PRINCIPAL

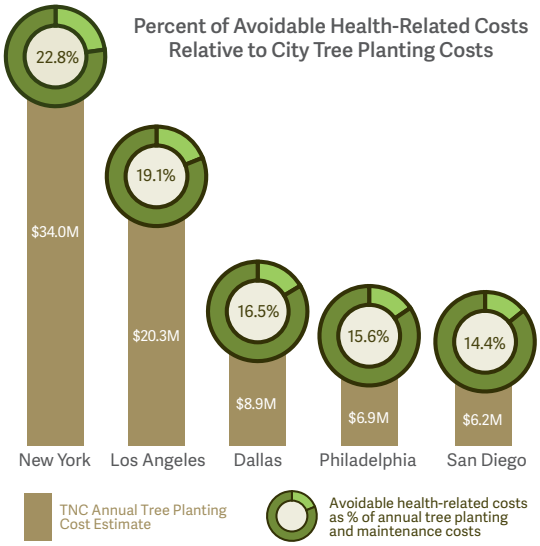
ERICH TRIESCHMAN,
SENIOR ANALYST

The trees in urban areas provide a wide range of health and economic benefits. However, most U.S. cities are experiencing a decline in urban forest cover. In a report with The Nature Conservancy (TNC) and the Trust for Public Land, *Funding Trees for Health: An Analysis of Finance and Policy Actions to Enable Tree Planting for Public Health*, Analysis Group calculated the avoidable health-related costs associated with planting additional trees – avoided costs that could be applied to help offset the costs of the new plantings themselves.

Trees serve as natural filters to lower PM pollution, which is linked to a number of respiratory and cardiovascular conditions. These conditions can result in increased hospital and emergency room visits, which raise medical costs, and may also interfere with employee productivity, causing lost or restricted work days. Increased tree planting could help reduce these types of health-related costs for patients, employers, and insurers.

To estimate the avoidable health-related costs from additional tree planting in 27 cities across the country, Analysis Group used a standard industry tool, the Co-Benefits Risk Assessment (COBRA) model. While tree planting and maintenance costs and avoidable health-related costs vary by city, Analysis Group determined that additional tree plantings in the most effective 20% of available city locations could reduce costs related to respiratory and cardiovascular conditions.

These savings amount to substantial percentages of the tree planting and maintenance costs estimated by TNC for different cities – for example, 23% in New York and 19% in Los Angeles. (See figure.) The report estimates that maintaining the current urban canopy would require an additional investment of around $1.87 per person annually. An additional investment of $5.87 per person annually would allow cities to expand the canopy significantly, leading to the potential health benefits measured by Analysis Group.



Notes: Tree planting cost estimates are based on data from 2014, and avoidable health-related costs are based on data from 2010. Results do not reflect recent natural events.

Municipalities that are looking for new sources of funding for tree planting may find an unlikely ally in health care companies and employers seeking innovative solutions for lowering health-related costs. Conducting further analysis could help cities make decisions about local tree planting scale and locations that would have the greatest impact on health-related benefits and costs. ■

Recent Conferences

In 2017, Analysis Group contributed to the following major conferences through sponsorships, poster presentations, and participation in symposia and on panels. For more details on these and other upcoming health care conferences, please visit our website.

ISPOR 20th Annual European Congress

November 2017

- Symposium: Evaluating survival benefits in technology appraisals of innovative oncology drugs
- 12 research posters

PROMIS® in Action: Clinical and Research Implementations and Implications

October 2017

- Analysis Group was a sponsor of this international conference on optimizing and harmonizing the global use of PROMIS measures and related resources

Academy of Managed Care Pharmacy (AMCP) Nexus 2017

October 2017

- Posters included: Evidence-based treatment recommendations for Parkinson's disease psychosis; therapies for adults with attention-deficit hyperactivity disorder; cost effectiveness of treatment for non-small cell lung cancer; burden of care for patients with chronic hepatitis C

PAINWeek 2017

September 2017

- Poster: Abuse-deterrent opioids

33rd International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE)

August 2017

- Podium presentation: Advanced non-small cell lung cancer in elderly patients
- Posters included: Severe aplastic anemia; glioblastoma and approval of bevacizumab; perampanel initiation in epilepsy treatment; somatostatin analogs use and quality of life in patients with carcinoid syndrome

Cambridge Healthtech Institute's Next Generation Dx Summit 2017

August 2017

- Presentation: Developing dossiers for technical assessment of advanced diagnostics

Alzheimer's Association International Conference 2017

July 2017

- Presentation: Health service use and potentially avoidable hospitalizations prior to Alzheimer's disease diagnosis
- Presentation: Annual wellness visits and cognitive care

GCR Live IP & Antitrust California

May 2017

- Panel: Pharmaceutical pricing and public policy

ISPOR 22nd Annual International Meeting

May 2017

- Symposium: PRO measurements in health economic evaluations
- Research poster award finalists: Hepatitis A, B, and A/B vaccination series; carcinoid syndrome symptoms and quality of life; transfusion independence in severe aplastic anemia; health care resource utilization and costs among adult schizophrenia patients
- 10 additional posters

2017 Pharma Industry Summit

April 2017

- Panel: Value-based and innovative contracting/ reimbursement arrangements

4th Annual Business of Personalized Medicine Summit

March 2017

- Plenary session: Moving Targets: Strategies to prepare for reimbursement trends and changes in payment policies

AMCP Managed Care & Specialty Pharmacy Annual Meeting

March 2017

- Bronze medal-winning posters included: A review of Medicare data on therapy for advanced renal cell carcinoma; real-world treatment patterns and costs in leukemia patients; refill gaps and dose reductions in patients with prostate cancer; drug interactions in patients treated with abiraterone acetate plus prednisone or enzalutamide

Analysis Group Expert David Dranove Highlighted in Historic Health Care Merger Review

In what was widely considered to be the largest proposed merger ever in the health care industry, academic affiliate David Dranove of Northwestern University's Kellogg School of Management served as the expert economist for the U.S. Department of Justice (DOJ) in its successful challenge of Anthem's acquisition of Cigna. The two companies are among the five largest health insurers in the United States. Supported by a team of Analysis Group consultants, Professor Dranove submitted two expert reports, testified twice in deposition, and testified four times in court on the issues of market definition, the impact of the proposed transaction on market concentration, and the impact of the proposed transaction on competition.

The most prominent feature of Anthem's case was its "robbing Peter to pay Paul" theory of the case. Anthem argued that the transaction would enable the merged entity to extract or negotiate lower payments to providers (thereby "robbing Peter"), and that the benefits of these payment reductions would flow to self-insured employers (thereby "paying Paul"). Professor Dranove's analysis and testimony showed that lessening competition on the insurer side of the market in order to counter market power on the provider side of the market made little economic sense; promoting competition on both sides of the market is necessary for "bending the cost curve." Firmly grounded in the economics of business strategy – based on how insurers actually compete and how health care markets actually work – Professor Dranove's framework tied together the upstream and downstream, as well as the static and dynamic, elements of the transaction.

The successful challenge to the merger preserved competition in a very important sector of the U.S. economy and – more generally – avoided setting a precedent in which a lessening of competition upstream can be considered a merger-specific efficiency. As a result of this work, Professor Dranove was selected as a 2017 Honoree for Outstanding Antitrust Litigation Achievement in Economics by the American Antitrust Institute. ■

For the digital edition, including exclusive online content, visit www.analysisgroup.com/health-care-bulletins.