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Imperative: Comparative Effectiveness Research

Pressures by government and private payers on biopharmaceutical companies to establish the value of their products presents the necessity to develop outcomes data which will affect all aspects of the biopharma product lifecycle. By Morgan Lewis & Bockius partner Stephen Paul Mahinka.

Structural Changes in Biopharmaceutical Industry Stimulating Comparative Effectiveness Research

For most of the existence of the modern biopharmaceutical industry, the selection of potential candidates for research and development, determinations of pricing for products, and marketing have been divorced from comparative effectiveness considerations. With the inexorable rise globally of healthcare expenditures, coupled with pressures on national healthcare budgets and the expansion of healthcare insurance and coverage, traditional modes of operation are increasingly not possible for the biopharmaceutical industry. Whether referred to as comparative effectiveness research (CER), outcomes research, pharmacoeconomics, or healthcare technology assessment (HTA), the imperative is clear: Biopharma companies must incorporate cost- effectiveness and value-demonstration data at all levels of the product lifecycle.

There are numerous, mutually-reinforcing, structural changes in the global biopharmaceutical industry environment that have created this substantially-enhanced focus on cost-containment mechanisms. Among the principal driving changes are:

- Demographic changes, significantly increasing demand for biopharmaceutical products. Among the industrialized nations, in Europe, the US, and Japan, changing demographics, with an increasingly aging population that traditionally demands provision of much greater levels of healthcare products and services;
- Globally, a significantly decreased capability to pay for the rise of demand for healthcare products and services in view of reduced economic growth; and
- The continued rise in prices of many biopharma products, especially in areas such as oncology,[1] as the recent protest by a group of oncologists regarding pricing of Sanofi's Zaltrap, which led to a 50% reduction in the product's price;[2]
- In the US, the expansion of healthcare insurance coverage to approximately 30 million people by the Patient Protection and Affordable Care Act of 2010 (PPACA, or "Obamacare"); and
- In the US, the continuing shift of over 70 million people in the baby-boom generation to over 65 years old (which began in 2011).

These structural shifts have been accompanied by other developments, some statutory and others reactions to statutory changes, including consolidation among biopharma industry customers intended in part to assist in negotiating for price reductions. These increasing pressures to develop and utilize CER are expected to have a "substantial impact" within the next three to five years, according to one recent survey.[3]

In the US, numerous changes made by PPACA were intended to address this increased demand for products and services through a combination of initiatives that have the potential to impose demand levels and pricing/payment restrictions. These include:

- Stimulating comparative effectiveness research;
- Creation of a regulatory approval pathway for biosimilars;
- Creation of the Independent Payment Advisory Board (IPAB), charged with focusing on control of Medicare expenditures;
- Creation of the Patient-Centered Outcomes Research Institute (PCORI), charged with focusing on CER;
- Stimulating the development and use of standardized quality of care / quality of service guidelines by healthcare providers;
- Stimulating the use of healthcare information technology by healthcare providers to manage/reduce demand and increase efficiency; and
- Stimulating the development and use of hospital / physician practices combination entities to reduce demand and prices for healthcare products and services and increase efficiency, termed Accountable Care Organizations (ACOs).

PPACA and Comparative Effectiveness Research

PPACA contains several provisions directly supporting the development of CER concerning healthcare products and services. A new entity, established under Section 6301 of PPACA, is the PCORI, which is intended to assist in conducting CER and disseminating research findings. PCORI is charged with identifying national priorities, establishing a methodology committee, and developing a research project agenda for CER.

Because of biopharma industry concerns that PCORI would be used essentially as a price-reduction entity, PPACA required that PCORI's CER "findings not be construed as mandates for practice guidelines, coverage recommendations, payment, or policy recommendations" This directive, however, is limited only to government use of the findings. Private payers can use PCORI's findings as a basis for their product or service approval or reimbursement decisions. This difference has the clear potential to allow for implementation of CER sponsored by PCORI notwithstanding the ostensible prohibition of any such consequences from cre-

ation of the entity. Of further concern to the industry are statements, such as by the head of PCORI, that while PCORI will not focus on cost effectiveness, "cost analysis" is undefined in PPACA, and patients will decide whether PCORI will fund research regarding costs and healthcare outcomes.[4] Indeed, PCORI has undertaken a plan to fund CER in certain specific areas, such as the treatment of uterine fibroids, in addition to its general methodological research, furthering concerns that the entity will develop into a cost reduction mechanism through its sponsored research.[5] PCORI recently announced its first head-to-head comparative effectiveness drug trial, involving inflammatory bowel drugs.[6]

Notwithstanding the stated limitations on government use of CER set out in PPACA, the statute does allow the Centers for Medicare and Medicaid Services (CMS) to use CER results to make a determination concerning Medicare coverage if (1) such use is through an iterative and transparent process and (2) a determination to deny Medicare coverage for a product or service is not based solely on CER. These aspects of the statute raise industry concerns that CER could be used by CMS if the agency is careful to incorporate its use within these parameters.

This potential for expanded governmental use of CER has been exacerbated by suggestions by other agencies about promoting use of CER, such as the Agency for Healthcare Research and Quality's proposal to encourage use of "academic detailing" to disseminate CER to healthcare providers,[7] assertedly to counter biopharma industry promotional activities. As a consequence, the American Medical Association (AMA) remains concerned that PCORI will apply CER using cost analysis, and has opposed any such activities in its comments to PCORI on the definition of "outcomes research".[8] By contrast, the American Hospital Association has proposed using CER, including cost analysis, to improve healthcare quality and efficiency.[9]

Potential Limitations on Use of CER

CER clearly has great promise for use by government and private payers in establishing price and payment restrictions. However, there are significant practical limitations on the use of CER in pricing and reimbursement decisions. These include the absence of accepted research protocols for CER, the absence of a critical mass of historical CER studies for comparison purposes that have been conducted in accordance with acceptable and defensible research protocols, and significant controversy within the scientific community regarding the proper interpretation of CER results. With respect to biopharma products, for example, CER data was available for only about half of the new drugs approved by the Food and Drug Administration (FDA) over the past decade.[10] Such limitations raise significant concerns regarding the practicality and propriety of government or private payers using CER for pricing/reimbursement decisions absent greater definition of "appropriate and acceptable research" and an enhanced database of CER.

Further, as with any efforts to limit access to healthcare products or services, the application of CER to do so can be expected to generate substantial opposition in many circumstances. The potential for controversy is illustrated by the substantial public opposition to the 2009 recommendations by the US Preventive Services Task Force to end routine mammograms for women in their 40s, on the asserted basis of a failure to establish that such tests were necessary, which resulted in reversal of the recommendation.

In addition to these potential limitations, FDA's traditional hostility to use and dissemination of CER also may provide restrictions on practical use of results, particularly for CER generated and disseminated by biopharma industry companies. FDA traditionally has required two comparative clinical studies for cost or comparative effectiveness claims. Notwithstanding the direction under Section 114 of the FDA Modernization Act of 1997, amending the Food, Drug, and Cosmetic Act, for FDA to provide guidance regarding the proper scope of communication of healthcare economic information to formulary committees, the Agency has not do so, providing no guidance either on what constitutes "substantial clinical experience" as a potential basis for promotion of products or on what constitutes proper "scientific exchange."[11] FDA's senior drug review official has repeatedly expressed skepticism of CER in recent years, and the need to adhere to FDA's traditional requirement of comparative clinical studies as the basis for any marketing claims.[12]

FDA thus has required a very high level of evidence—comparative clinical trial—to support claims based on CER. For insurers' formulary committees and other healthcare technology assessment entities, however, there is a perceived utility of and acceptability of CER based on other elements, such as accepted methods of pharmacoeconomics such as econometric analysis and nonclinical trials-based outcomes research. This demand for CER from biopharma products manufacturers, coupled with the desire to expand use of CER by those government agencies responsible for product reimbursement, may influence FDA to adapt its historic approach and allow use of non-clinical trials-based CER in marketing and promotion.

Some potential for evolution of FDA's traditional approach was suggested by recent public statements by a reviewer in the FDA's Center for Drug Evaluation and Research that social media can be used to help validate the content of patient-reported outcomes to support labeling claims.[13] The potential for development of parallel reviews by FDA and CMS that may include consideration of CER also should be monitored, although there has been little progress in this direction. The agencies proposed a pilot Parallel Review program to conduct overlapping FDA premarket reviews and CMS national coverage determinations for certain innovative products, when sponsors agree.[14] The agencies suggested, in their Notice, that the proposed Parallel Review process "could also create incentives for venture capitalists and companies to increase their investment in innovative products by reducing the time to return on investment for those products eligible for parallel review."[15] Similarly, the potential uses of CER in determinations by other governmental/scientific entities affecting product use should also be monitored. For example, a decision by the Centers for Disease Control's Advisory Committee on Immunization Practices to limit the recommendation for vaccinating adults against hepatitis B to those under age 60 was assertedly based on cost effectiveness considerations.[16]

Use of CER to Affect Biopharma Pricing and Reimbursement

Notwithstanding FDA reluctance to support expanded use of CER, and the slow development of CER through PCORI, private payers in the US are aggressively mov-

ing to utilize CER in their decisions regarding pricing and reimbursement. For example, a large healthcare insurer, WellPoint, has released its own standardized CER guidelines for use in its evaluations of drug coverage.[17] Another large insurer, United Healthcare, has suggested that CER will foster the broader use of copay structures that discourage patients from seeking higher cost treatments that offer no real benefit over use of lower-cost drugs.[18] Similar to Wellpoint, the United BioSource unit of a large pharmacy benefits manager, Medco, has developed 13 principles for conducting comparative effectiveness research.[19] From the medical device context, Medtronic has entered into an agreement with another large healthcare insurer, Aetna, to provide economic data in support of purchase of its products.[20] All of these initiatives illustrate the increasing focus by US private payers on the potential use and increasing importance of CER in assisting with their payment and reimbursement decisions.[21] Further, a recent study concluded that CER would be very useful in assessing patient outcomes through "understanding the clinical value of existing treatments of known efficacy."[22]

Use of CER has been incorporated earlier and more broadly in coverage and payment decisions internationally. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) has made numerous decisions denying coverage using CER, including:

- a decision not to recommend use of Takeda's bone cancer drug Mepact, based on its cost-effectiveness criteria, even though it stated that the drug "might represent a potentially valuable new therapy;"[23]
- rejection of Bristol-Myers Squibb's Yervoy on cost-effectiveness grounds;[24]
- rejection of GlaxoSmithKline's Benlysta on cost-effectiveness grounds;[25]
- proposed rejection of Sanofi's new bowel cancer drug Zaltrop as not cost effective, while acknowledging clinical effectiveness;[26] and
- rejection of Savient's gout treatment Krystexxa on the basis of its "very high cost compared with the known benefit.[27]

NICE has rejected more than 60% of new cancer drug applications since the beginning of 2011.[28]

Other European Union healthcare technology assessment (HTA) organizations also have become increasingly active in utilizing CER, for example, through the creation of a new cost and comparative effectiveness—based system for review of healthcare products in Germany (conducted by the Institute for Quality and Efficiency in Healthcare),[29] and the establishment in France of a subgroup (CEESP) similar to NICE in its reimbursement authority over healthcare products. Other nations, including Canada, Australia, and recently Taiwan,[30] also have established entities similar in purpose and operation to NICE. A recent study suggests that the consequence of such HTAs using CER has been price reductions compared to US levels.[31]

Implications of Incorporation of CER in Lifecycle Management

The increasing utilization of CER by government and private payers presents several important implications for product lifecycle management for biopharma companies:

1. It is highly advisable to incorporate outcomes research into clinical trials to provide a strong basis for obtaining formulary acceptance and to enable marketing and promotion of the product to government and managed care payers.[32]
2. It is advisable for biopharma product developers to have discussions with payers at the clinical development stage concerning what CER might be necessary and appropriate to develop to support a positive coverage and reimbursement decision.
3. The potential for a reduction in the expected rate of return on product investment by reason of the increased use of CER should be incorporated into product candidate investment and R&D decisions, which assessment should include the increased costs by reason of CER evidence development.
4. The utility and desirability of developing nonclinical trials-based CER to support payment and reimbursement should be evaluated, for example, by pharmacoeconomics studies of value.
5. Consideration of forming partnerships with insurers and other payers to enhance development of appropriate data to support positive coverage/payment decisions, as Pfizer has done with Medco and AstraZeneca has entered into with WellPoint.[33]
6. Development of integrated market access cross-functional operations to effectively generate, manage, and apply CER from the drug and biologic development stage, through reimbursement and market access negotiations, to marketing and promotion, as well as across national boundaries.
7. Consideration of the potential of personalized medicines to enhance the likelihood of payer acceptance.[34]
8. Evaluation of the potential use of CER in later stages of the product lifecycle to support new indications and to support the product in competition with other products or therapies.
9. Consideration of company strategy with respect to potential negotiations with or demands by government or private payers regarding refunds or other pay-for-performance approaches to obtain formulary approval.

Novel Private Litigation Challenges to Biopharma Marketing and Promotion with CER

As discussed above, there is an increasing and unavoidable demand by government and private payers for CER data to support coverage and reimbursement determinations. The need by biopharma companies to develop and disseminate such CER data as part of drug and biologic marketing and promotion presents difficult issues regarding FDA's traditional enforcement approach.

In addition to the risk of FDA enforcement, it is important for biopharma companies to be aware of recent novel private litigation challenges to the use of CER in marketing and promotion. Claims have been brought by aggrieved competitors on various bases, including false advertising under the Lanham Act, state unfair competition and deceptive practices statutes, defamation, injurious falsehood, and tortious interference. These actions all seek to avoid direct challenges based on violations of the Food, Drug, and Cosmetic Act or FDA's regulations, since there is no private right of action under the act. The challenges have been based on marketing and promotion activities in a wide range of contexts, including publication of CER in peer-reviewed scientific journals, presentations of CER at scientific meetings, press releases, submissions to payers, and presentations by sales forces.

Three new, novel litigation challenges have been filed by competitors to the use and dissemination of CER:

- *ONY Inc. v. Cornerstone Therapeutics and Chiesi Farmaceutici* (W.D.N.Y., filed 2011) (dismissed on the basis that the CER study is a statement of scientific opinion, not a statement of facts; appeal dismissed by the Second Circuit, 2013), challenging publication of CER in a peer-reviewed scientific journal);[35]
- *Genzyme Pharmaceuticals v. Shire plc* (D. Mass., filed 2012) (denial of motion to dismiss), challenging issuance of a press release describing the results of a head-to-head clinical trial with the plaintiff's product, alleging the study was conducted for a different principal purpose; and
- *Ferring Pharmaceuticals v. Watson Pharmaceuticals* (D.N.J., filed 2012), challenging allegedly false comparative statements at public presentations by a consultant, including regarding a patient survey, concerning the plaintiff's product.

The increasing development and dissemination of CER in response the demands of government and private payers can be expected to give rise to more of such competitor litigation in the future. Consequently, CER should be carefully reviewed to ensure it is developed in accordance with prevailing scientific standards, and is disseminated either by including the entire article as published, with any summaries, press releases, or oral presentations focused on a factual recounting of the CER results.

Consequences of CER for Biopharma Growth and Investment

Cost-effectiveness research presents significant challenges for decisions regarding biopharma product development, promotion, investment, and mergers and acquisitions. Significant factors that will substantially affect payment and reimbursement include the potential for restrictions on Medicare or Medicaid coverage and reimbursement, and the potential of CER to mitigate such adverse consequences. Regardless of the status and use of CER by government payers, the acute interest by private payers illustrate that CER will increasingly be a crucial entry requirement for coverage and reimbursement for them, which biopharma manufacturers will have to address. Notwithstanding this emerging demand for CER, however, there is a significant potential for government enforcement action, primarily from FDA, from the use of CER in marketing and promotion. In addition, risks of competitor litigation challenging the dissemination of CER and its validity is also emerging as a significant potential risk to be addressed by biopharma manufacturers and product developers.

These risks unavoidably present additional uncertainty regarding valuation of product candidates for research and development expenditures, and for decisions regarding potential investment, licensing and other collaboration agreements, and M&A for products and companies.

Consequently, there is a much-heightened need to closely monitor and quickly adapt to regulatory and market changes and enforcement and litigation risks concerning the use of CER to properly assess payment and market access and sales expectations and undertake more informed valuations in making development, promotion, investment, and acquisition decisions.

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1 See P. Neumann, et al., "Therapies for Advanced Cancers Pose a Special Challenge for Health Technology Assessment Organizations in Many Countries," 31 Health Affairs 700 (April 2012)
2 Scrip, May 10, 2013
3 See D. Leonard, "CER 'Substantial Impact' Expected in Three-to-Five Years: NPC's [National Pharmaceutical Council] Annual Comparative Effectiveness Survey," RPM Report (March 2013)
4 Inside CMS, Sept. 29, 2011
5 Pink Sheet, Dec. 3, 2012
6 Pink Sheet, May 13, 2013
7 See M. Fischer and J. Avorn, "Academic Detailing Can Play a Key Role in Assessing and Implementing Comparative Effectiveness Research Findings," 31 Health Affairs 2206 (Oct. 2012)
8 Pink Sheet, Sept. 5, 2011.
9 Inside CMS, Nov. 10, 2011
10 J. of Am. Med. Ass'n, May 4, 2011
11 See, e.g., J. Griffin, et al., "Regulatory Requirements of the Food and Drug Administration Would Preclude Product Claims Based on Observational Research," 31 Health Affairs 2188 (Oct. 2012); A. Kesselbaum and J. Avorn, "The Food and Drug Administration has the Legal Basis to Restrict Promotion of Flawed Comparative Effectiveness Research," 31 Health Affairs 2200 (Oct. 2012); E. Perfetto, et al., "Communication About Results of Comparative Effectiveness Studies: A Pharmaceutical Industry View," 31 Health Affairs 2213 (Oct. 2012).
12 See R. Temple, "A Regulator's View of Comparative Effectiveness Research," 9 Clinical Trials 56 (Feb. 2012)
13 Pink Sheet, June 3, 2013.
14 See 75 Fed. Reg. 57045 (Sept. 17, 2010)
15 Recently, Medtronic announced that its renal denervation device was one of the first products to be accepted for review under the Parallel Review program. See Regulatory Focus, March 7, 2013.
16 Pink Sheet, October 31, 2011
17 Pharmaceutical Law & Industry Report, May 25, 2010
18 Pink Sheet, October 25, 2010
19 Pink Sheet, March 26, 2012
20 Gray Sheet, May 28, 2012
21 A recent report by IMS Health concluded that "real-world evidence" is increasingly influencing how payers are making biopharma coverage and reimbursement decisions, summarized in the Pink Sheet, May 27, 2013.
22 M Olfson & S. Marcus, "Decline in Placebo-Controlled Trial Results Suggests New Directions for Comparative Effectiveness Research," 32 Health Affairs 1116 (June 2013)
23 Scrip, Oct. 15, 2010
24 Scrip, Oct. 21, 2011
25 Scrip, May 4, 2012
26 Reuters, June 21, 2013
27 Scrip, Feb. 15, 2013
28 Pink Sheet, Jan. 14, 2013
29 Pink Sheet, Feb. 6, 2012
30 Scrip, Jan. 25, 2013
31 See J. Cohen, et al., "Compared to US Practice, Evidence-Based Reviews in Europe Appear to Lead to Lower Prices for Some Drugs," 32 Health Affairs 762 (April 2013)
32 Note the comments stressing that CER needs to be incorporated early in the product development pipeline by the head of CER at Novartis Pharmaceuticals, summarized in the Pink Sheet, Dec. 12, 2011, and by the director of public policy at GlaxoSmithKline, summarized in the Pink Sheet, April 9, 2012
33 Pink Sheet, November 14, 2011
34 AstraZeneca has noted its focus on personalized medicine as partly intended to enhance cooperation with and decisions by managed care payers, as noted in Scrip, October 21, 2011
35 The author and his firm are counsel for the manufacturer defendants in this action.