

Comparative Effectiveness Research: Impact on Biopharmaceutical Development, Pricing, and Promotion



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Structural Changes in Biopharmaceutical Industry Stimulating Comparative Effectiveness Research

- Structural changes in the biopharmaceutical industry environment enhance focus on cost-containment mechanisms
- Changes include:
 - **Demographic changes, increasing demand for pharmaceutical products**
 - Expansion of healthcare insurance coverage to approximately 30 million people by the Patient Protection and Affordable Care Act of 2010 (PPACA)
 - Shift of over 70 million people in baby-boom generation to over 65 beginning in 2011)
 - **Integration of healthcare insurers with providers**
 - **Buyer consolidation – Accountable Care Organizations (ACOs)**
- Resulting pressure from both governmental and private payors to address this increased demand through access and/or payment restrictions

Changes by PPACA Affecting Demand Levels and Prices/Payments

- Stimulating comparative effectiveness research (by both government and private payors)
- Creation of biosimilars regulatory approval pathway
- Creation of Independent Payment Advisory Board (IPAB)
- Creation of Patient-Centered Outcomes Research Institute (PCORI)
- Stimulating use of quality of care/service guidelines by healthcare providers
- Stimulating use of healthcare information technology to manage/reduce demand
- Stimulating use of provider/physician practices/insurer combined entities to manage/reduce demand (accountable care organizations (ACOs))

PPACA and Comparative Effectiveness Research

- PPACA contains provisions supporting the development of comparative effectiveness research (CER) concerning healthcare products and services
- Section 6301 establishes the Patient-Centered Outcomes Research Institute (PCORI) to assist in conducting CER and disseminating research findings
 - PCORI is to identify national priorities, establish a methodology committee, and establish a research project agenda
- PCORI is required to ensure that CER “findings not be construed as mandates for practice guidelines, coverage recommendations, payment, or policy recommendations”
 - Private payers can, however, use such findings as a basis for their product or service approval or reimbursement decisions
 - Head of PCORI has stated PCORI will not do CER, but noted “cost analysis” is undefined, and patients will decide whether PCORI will fund research regarding costs and healthcare outcomes (Inside CMS, Sept. 29, 2011)
 - PCORI has undertaken a plan to fund CER in certain specific areas (e.g., treatment of uterine fibroids), in addition to methodological research. (Pink Sheet, Dec. 3, 2012)

PPACA and Comparative Effectiveness Research

- PPACA allows Centers for Medicare and Medicaid Services (CMS) to use CER results to make a determination concerning Medicare coverage if such use is (1) through an iterative and transparent process, and (2) a determination to deny coverage is not based solely on CER
 - Agency for Healthcare Research and Quality proposed use of “academic detailing” to disseminate CER to healthcare providers ([Pink Sheet](#), April 26, 2010)
 - [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)
 - The American Medical Association remains concerned that PCORI will apply CER using cost analysis, and opposed such activities in its comments to PCORI on definition of outcomes research. ([Pink Sheet](#), Sept. 5, 2011).
 - By contrast, the American Hospital Association has proposed using CER, including cost analysis, to improve healthcare quality and efficiency ([Inside CMS](#), Nov. 10, 2011)

Potential Effects of CER on Biopharma Pricing and Reimbursement

- Significant practical limitations on use of CER in pricing and reimbursement decisions, including absence of accepted protocols, lack of historical CER studies for comparison, and controversy as to interpretation of results
 - Comparative effectiveness data was available for only about half of new drugs approved by FDA over the past decade (J. of Am. Med. Ass'n, May 4, 2011)
 - Raises concerns regarding practicality or propriety of using CER for pricing/reimbursement decisions
- Potential for controversy – e.g., rejection of 2009 recommendations by U.S. Preventive Services Task Force to end routine mammograms for women in their forties

Potential Effects of CER on Biopharma Promotion -- FDA Issues

- Potential for FDA restrictions on dissemination of comparative effectiveness research
 - FDA traditional requirement of two comparative clinical studies for claims
 - Absence of FDA guidance under Section 114 of FDA Modernization Act of 1997 for communication of healthcare economic information to formulary committees
 - Absence of FDA guidance of “substantial clinical experience” as a potential basis for promotion of products
 - Absence of FDA guidance on what constitutes proper “scientific exchange”
 - 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. Peretto, et al., “Communication About Results of Comparative Effectiveness Studies: A Pharmaceutical Industry View,” 31 Health Affairs 2213 (Oct. 2012).

CER – Monitor Potential Applications

- Monitor potential for parallel reviews by FDA and CMS that may include consideration of CER
 - Proposed pilot program by FDA and CMS to conduct overlapping FDA premarket reviews and CMS national coverage determinations for certain innovative products when sponsors agree. See 75 Fed. Reg. 57045 (Sept. 17, 2010)
 - The Agencies suggest, 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”
- Monitor potential uses of CER in determinations by other governmental/scientific entities affecting product use
 - e.g., decision by Centers for Disease Control’s Advisory Committee on Immunization Practices to limit recommendation for vaccinating adults against hepatitis B to those under age 60 based on cost effectiveness considerations. (Pink Sheet, October 31, 2011)

Potential Effects of CER on Biopharma Pricing and Reimbursement

- Potential for significant impact of CER on drugs/biologics access and reimbursement
 - Note study of Australian drug market by Tufts University Center for the Study of Drug Development, concluding that “comparative effectiveness research severely restricts access to drugs not deemed cost-effective” ([Life Sciences Law and Industry Report](#), July 16, 2010)
- Potential effects on product purchasing – first comparative effectiveness trial of two pioneer drugs by National Institutes of Health
 - Comparative NIH trial of two Genentech drugs (Lucentis - \$2,000/dose and Avastin - \$40/dose) -- results showed both equally effective at treating an eye disease ([Pink Sheet](#), May 9, 2011)
 - Office of Inspector General of HHS subsequently concluded Medicare Part B could have saved \$1.1 billion by substituting Avastin for Lucentis ([OIG Report](#), Sept. 7, 2011)
 - Subsequent study confirmed substitution cost-effective, but with safety questions regarding Avastin use in macular degeneration context ([Pink Sheet](#), May 7, 2012)
 - Reduction in price of Zaltrop by Sanofi (of 50%) following Memorial Sloan-Kettering Cancer Center decision not to provide the drug to its cancer patients due to its cost relative to Avastin, and alleged absence of clinical superiority data ([Pink Sheet](#), Dec. 24, 2012)

Potential Effects of CER on Biopharma Pricing and Reimbursement

- Private payors moving to apply CER regardless of status of government activity
 - WellPoint released its own standardized CER guidelines for use in its evaluations of drug coverage. (Pharmaceutical Law & Industry Report, May 25, 2010)
 - United Healthcare has suggested that CER will foster broader use of co-pays that discourage use of lower-cost drugs. (Pink Sheet, October 25, 2010)
 - United BioSource unit of Medco has developed thirteen principles for conducting comparative effectiveness research. (Pink Sheet, March 26, 2012).
 - Medtronic agreement with Aetna to provide economic data in support of purchase of its products (Gray Sheet, May 28, 2012)

CER – Monitor International Applications

- Monitor assessments by EU Member nations and the U.K.'s National Institute for Healthcare and Clinical Excellence (NICE) and their application of CER
 - e.g., NICE 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." (Scrip, Oct. 15, 2010).
 - e.g., NICE rejection of Bristol-Myers Squibb's Yervoy melanoma drug as not cost-effective. (Scrip, Oct. 21, 2011)
 - NICE rejection of GlaxoSmithKline's Benlysta on cost effectiveness grounds. (Scrip, May 4, 2012)
 - NICE has rejected over 60% of new cancer drug applications since the beginning of 2011. (Pink Sheet, Jan. 14, 2013)
 - Establishment of new comparative effectiveness-based system for healthcare products in Germany (AMNOG)
 - Establishment in France of sub-group (CEESP) similar to NICE in its reimbursement authority.

Incorporation of CER in Lifecycle Management

- CER raises several issues regarding product lifecycle management for biopharma companies
 - Incorporate outcomes research into clinical trials to provide bases for marketing and promotion of product to government and managed care payors
 - Potential discussions with payors concerning CER at clinical development stage
 - Potential for reduction in return on product investment by use of CER
 - Increased costs for clinical CER trials
 - Adverse effects on R&D budget for potential other new products
 - Development of non-clinical trials-based CER to support payment and reimbursement
 - Partnerships with drug companies and managed care entities to support coverage/payment decisions
 - e.g., Pfizer/Medco and AstraZeneca/WellPoint data development partnerships ([Pink Sheet](#), November 14, 2011)

Incorporation of CER in Lifecycle Management

- Development of integrated market access cross-functional operations by drug companies to effectively generate, manage, and apply CER from drug development stage, through reimbursement and market access negotiations, to marketing and promotion, and across national boundaries
- Possible focus on development of personalized medicines to potentially enhance likelihood of payor acceptance of proposed pricing
 - e.g., AstraZeneca focus on personalized medicines to enhance cooperation and decisions with managed care payors (Scrip, October 21, 2011)
- Potential use of CER in later stages of product lifecycle to support new indications and to defend product from competing products or therapies

Incorporation of CER into Product Marketing and Promotion

- Incorporation of CER into drug marketing and promotion raises difficult issues concerning FDA regulation
 - CER-based claims (pharmacoeconomics claims) are regulated under FDA's general labeling and advertising provisions
 - Historically, FDA has required two "adequate and well-controlled studies," ordinarily head-to-head trials, to support comparative effectiveness claims
 - Federal Trade Commission (FTC) has similarly focused on adequate scientific evidence supporting comparative drug claims
 - Pharmacoeconomics claims unlikely to be solely clinical trials-based
- In response to likely increased use of pharmacoeconomics claims based on CER, FDA requested public comment on a proposed study of comparative advertising of prescription drugs. See 76 Fed. Reg. 36663 (July 1, 2011)
- Need to incorporate claims based on CER in marketing and promotion, and on pricing, reimbursement, and market access to payors, but in the absence of clear guidelines
- Issues relating to inclusion of CER data in drug package insert/labeling

Potential for Private Litigation Challenges to Promotion with CER

- Emerging new private litigation challenges to use and promotion of comparative effectiveness research and claims
 - [ONY Inc. v. Cornerstone Therapeutics and Chiesi Farmaceutici](#) (W. D.N.Y.)
 - [Genzyme Pharmaceuticals v. Shire plc](#) (D. Mass.)
 - [In re: Rigel Pharmaceuticals Securities Litigation](#) (9th Cir.)
 - [Ferring Pharmaceuticals v. Watson Pharmaceuticals](#) (D. N.J.)
 - [Millennium Laboratories v. Ameritox](#) (D. Md.)
- Claims brought on various bases, including false advertising under the Lanham Act, state unfair competition and deceptive practices statutes, defamation, injurious falsehood and tortious interference claims
- Challenges from promotion in a wide variety of contexts, including publication of CER in peer-reviewed scientific journals, scientific meeting presentations, press releases, securities filings, submissions to payors, and detail force presentations

Consequences of CER for Biopharma Growth and Investment

- Cost effectiveness research presents significant challenges for biopharma product development, promotion, investment, and M&A
 - Potential for restrictions on Medicare or Medicaid coverage and reimbursement from comparative effectiveness research
 - Potential for adoption of similar or independent restrictions on coverage and reimbursement by private payors
 - Government enforcement and private litigation risks regarding promotion of cost effectiveness research
 - Consequent uncertainty regarding product and company valuation for product development, investment, licensing, and M&A
- Need to closely monitor and quickly adapt to regulatory and market changes and enforcement and litigation risks concerning use of CER, and payment and market access and sales expectations, concerning drugs and biologics in making development, promotion, investment, and acquisition decisions

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