Biosimilars Policy Forum: Perspectives on Safety and Efficacy of Future Products

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Based on the Forum on Regulation of Follow-On Biologics: Ensuring Quality and Patient Safety that was held at the National Press Club in Washington, DC, in April 2009, to review current issues related to biosimilars legislation. The forum was sponsored by the Jefferson School of Population Health, with a grant support from sanofi-aventis.

Things change quickly on Capitol Hill, and these changes can affect the course of new legislation. The Forum on Regulation of Follow-On Biologics was convened to discuss the implications of the current discussion on biosimilars legislation. Keynote Speaker Michael McCaughan, Editor of The Pink Sheet, FDC/Windhover Biopharma Group, reviewed the options for biosimilars regulation, noting that the new US Food and Drug Administration (FDA) biosimilars pathway being discussed in Congress remains in a long queue of major legislation pieces. McCaughan highlighted the emerging need for a new business model for drug manufacturers of biosimilars and outlined the roles of Senate Finance Committee Chairman Max Baucus (D-MT), Senate Health, Education, Labor, and Pensions Committee Chairman Edward Kennedy (D-MA), and House Energy Committee Chairman Henry Waxman (D-CA) as key figures in this legislative process.

Drug manufacturers and drug regulation have moved from a focus on large populations with low risk to smaller population cohorts with higher risks. User fees and reduced government financing have raised questions about the FDA's credibility and its independence from drug manufacturers. Drug and agricultural safety concerns have also increased, at a time when the United States has become more risk-averse.

Brian Harvey, MD, PhD, Vice President of Regulatory Policy, sanofi-aventis, reviewed the utilization of a comparative protocol strategy for a biosimilars regulation. Gundu H. R. Rao, PhD, University of Minnesota, discussed World Trade Organization agreements and the impact of globalization of economic and marketing practices that will necessitate a global review and approval process for biosimilars.

Unlike the small-molecule generics, biosimilars are complete biologic products, presenting new issues. The European Medicine Agency, the World Health Organization, and other organizations worldwide require or are leaning toward requiring clinical equivalence testing, because biosimilars may be similar but are not identical to the original product. Even manufacturing batch or lot variation requires definition by clinical experience; laboratory testing alone is not sufficient. Clinician perspectives on biosimilars focus on protecting public health and patient safety, arguing that it is essential that regulatory standards not be solely based on cost-comparisons.

Key legislative aide to Rep. Waxman, Ann Witt, reported intense lobbying and pressure from all sides in the biosimilars debate in Congress, highlighting the following points.

- Inconsistencies toward biologics and biosimilars:
  - The cost of biologics is driving concerns about open access
  - What will the future of the US drug supply look like?
  - Products must not be priced out of reach of patients
  - Regulation of simple proteins (human growth hormone, insulin) as drugs and other products as biologics.

- Current bills in Congress focus on the safety and efficacy of biosimilars and the need for an approval process:
  - Emerging science should guide legislation to allow the FDA to decide on approval and interchangeability
  - Bill must encourage science and allow for future knowledge to be applied; scientists, not Congress, must make scientific decisions
  - Safe and effective drug is still key
  - Biosimilars will spur innovation: monopoly on pricing is not good for competition
  - Comparability concerns; some manufacturers agree to forgo repeating clinical trials for the biosimilar product
  - While the Waxman-Hatch Act is celebrating its 25th anniversary, Rep. Waxman wants to ensure a biosimilar bill works as well as the generic bill.

- Avoid unnecessary procedural delays in process for biosimilars approval:
  - FDA does not write guidance in this early stage, when little is known about what works or does not.
  - Patent resolution should be handled quickly and effi-
ciently; need proper process to avoid legal delays.

Property protection—how much more intellectual property protection is needed versus patent protection:
• European Union not comparative because of price control versus unregulated US prices
• Need to extend patent protection if FDA approval is delayed, but not the same as exclusivity.

Professor Larry Kotlicoff of Boston University, a Teva Pharmaceuticals consultant, argued for a business need to recoup investment to allow for adequate profits along with competition in the marketplace. Promoting a balanced approach to marketing exclusivity, he said that continuing monopoly protection of biologics far into the future may block discoveries that would improve public health and undermine sales. Exclusivity, innovation, and patent protection should be balanced. Prolonged monopoly protection, noted Dr Kotlicoff, distorts consumer choice by maintaining artificially high prices. Reducing the costs of biologics limits their expenditure risk, but the question is whether we can increase economic efficiency. Biologics offer great promise for improving health and well-being, but how we ensure access for all Americans to these medications at affordable prices, within a reasonable period from their discovery remains the business question for health policy legislation.

Geno Merli, MD, Thomas Jefferson University Hospital, addressed the unintended consequences of interchangeability. He listed a clinician’s concerns in determining whether a biosimilar would be appropriate for a specific patient:
1. Which disease is being treated
2. Safety considerations for the specific product
3. Use current generics that are safe and effective or expand use to include biosimilars
4. Because of the nature of biologics, there is wide variation in their components, which include proteins, polysaccharides, glycosylated proteins, polynucleotides; these may also trigger the release of antibodies
5. The 2007-2008 heparin contamination illustrates some of the risks with biologic manufacturing/products, because of the different methods of preparation and ingredient supply chains
6. Immunogenicity of biosimilars remains difficult to detect and measure; clinicians cannot compare disparate published studies regarding this important safety concern on biologics or biosimilars.

Faculty Panel Discussion

Judith K. Jones, MD, PhD, Degge Group, addressed the many challenges in assessing the safety of biologics and biosimilars that also relate to their approval or monitoring, such as the lack of direct relationship to pharmacokinetics; pharmacoepidemiology methods used for drugs are not always applicable; and measuring exposure, dosing.

Finally, E. Randy Vogenberg, RPh, PhD, Biologic Finance and Access Council, expanded on the theme of unintended consequences, establishing that medications are part of managing risk—the health risk continuum of people from an economic and a clinical perspective. Specifically, 2 key issues around managing risk are (1) financing and insurance underwriting; and (2) benefit design.

In less than 7 years, biologics grew from 1% in 2000 to about 4% to 10% of pharmacy benefit drug spending in 2007. Claim spending for biologics is 4 to 10 times greater than for traditional, small-molecule drug coverage or on average 22 times higher cost per daily dose. Managed care experts expect that biosimilars will offer a smaller percent discount, because of manufacturing costs and reduced competition compared with traditional generics.

In 2008, specialty pharmacy spending was about 14% of total pharmacy cost, and this trend continues. In Medicare Part D, 90% of beneficiaries who use a specialty product hit the doughnut hole from various cost-sharing payments (copay, coinsurance, and deductible), with an average out-of-pocket expense of 12%.

Insurance modeling for financial risk management goes beyond patent and regulation discussions. In practice, drugs in the same therapeutic category with equivalent outcomes are considered therapeutically equivalent by the Centers for Medicare & Medicaid Services and by many other payers. Payers, for example, have established therapeutic equivalence for interferons, antibiotics, and growth hormones, but these are band-aid approaches for an out-of-date insurance and benefit design marketplace.

Conclusion

With the growth of biologics and diagnostics, we are moving into personalized medicine. Current insurance and benefit design will not accommodate branded or biosimilar biologics let alone individualized therapy.

There is a general agreement that good science must prevail in any biosimilars legislation, but the limits of science create gaps for the regulatory agencies, just as the economic recession is creating limits for business to fill needed gaps in our patient care armamentarium of biologic products. It is this uncertainty that is creating the worry of unintended consequences for Americans.