AARP
AFL–CIO
Altus Pharmaceuticals Inc.
American Society of Clinical Oncology
Amgen Inc.
Association of American Universities
Barr Pharmaceuticals Inc
Biotechnology Industry Organization
Biogen Idec
California Healthcare Institute
CalPERS
Coalition for a Competitive Pharmaceutical Market
Cell Therapeutics
Centers for Medicare & Medicaid Services
Consumers Union
Food and Drug Administration
Federal Trade Commission
Genentech, Inc.
General Motors Corporation
Glycomimetics, Inc.
Generic Pharmaceutical Association
Insmed Inc.
Johnson and Johnson
Millennium
Mylan Labs, Inc.
National MS Society
National Organization for Rare Disorders
National Venture Capital Association
NGA
Novartis/Sandoz
PhRMA
Teva Pharmaceutical Industry, Ltd
UAW
UnitedHealth Group
Vertex Pharmaceuticals

ONE HUNDRED TENTH CONGRESS

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

April 3, 2008

Dear :

Over the course of the last year, the Members of the Subcommittee on Health have heard from numerous stakeholders about creating a pathway to allow for the Food and Drug Administration (FDA) to approve generic biologic products. Generic versions of biologic products have the potential to lower costs and improve access to life-saving medicines for millions of American consumers. Accordingly, it is imperative that we find a path forward.

Members of the Subcommittee on Health are committed to this issue and several have introduced legislation to establish an abbreviated approval process. We have found it challenging, however, to reach consensus on a single bill that would accomplish this goal. In order for the Subcommittee to better evaluate the merits, benefits, and costs of a biosimilars bill, we wish to understand more fully the range of perspectives, concerns, and objectives that might be addressed in such a legislative proposal. We are also interested as to where consensus exists within the biotechnology community and among other stakeholders.

Therefore, we invite you to answer the attached questions. Your responses will help us to better understand the significant issues surrounding the biosimilars debate, and will assist us in our efforts to craft legislation. We ask that you please respond by no later than Tuesday, April 22, 2008. Please endeavor to respond in as concise a manner as possible, without inclusion of extraneous materials. We recommend that in addition to mailing your responses to the Committee on Energy and Commerce, Room 316 Ford House Office Building, Washington, D.C. 20515, that you also send a copy of your responses by e-mail to Melissa Sidman with the Committee staff at melissa.sidman@mail.house.gov. Ms. Sidman can be reached at (202) 226-2424.

We thank you for your assistance in this effort and look forward to receiving your input on this potentially significant health policy measure. If you have questions or need further information, please contact Robert Clark with the Committee on Energy and Commerce staff at (202) 225-2927 or John Little with Rep. Nathan Deal's office at (202) 225-5211.

Sincerely,

Frank Pallone, Jr.
Chairman
Subcommittee on Health

Nathan Deal
Ranking Member
Subcommittee on Health

Attachment

cc: The Honorable John D. Dingell, Chairman
Committee on Energy and Commerce

The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

Science/Safety

1. What is immunogenicity? Why is immunogenicity a special concern for biologics and what are the risks to patients? Do immunogenicity risks vary depending on the type of biologic?

2. To what degree, if any, is immunogenicity testing necessary? Should immunogenicity testing be mandated by statute for all follow-on biologics (FOBs) or should the Food and Drug Administration (FDA) be given discretion to determine whether such studies, and what types of studies, are needed on a case- by-case basis?

3. Has FDA exercised appropriately its discretion whether to require immunogenicity testing for manufacturing changes? Should immunogenicity testing for manufacturing changes be mandated by statute, or should FDA be given discretion to determine whether such testing is necessary?

4. Should FOB applicants have to provide evidence of similarity, safety, and effectiveness of each indication separately or can evidence for one indication be extrapolated to another?

5. Under the Food and Drug Administration Amendments Act of 2007, Congress established new authorities for FDA to enforce drug safety. How should the new post-market authorities enacted in this legislation be applied to FOBs? Are post-market studies always needed for FOBs? Are there situations in which FOB applicants will need to conduct post-market studies that are different from those that have been required and/or requested for the reference product?

6. Should non-interchangeable FOBs be required by statute to have different non-proprietary names from the reference product? What should the standard be for interchangeable FOBs? What are the advantages and disadvantages of requiring different non-proprietary names, including any affect on patient safety? What alternatives are available?

7. Is it important that an innovator and an FOB have the same mechanism of action? Why or why not? If the mechanism of action of the reference product is unknown, should the FOB applicant be required to determine the mechanism of action and ensure that both products share the same one? Why or why not?

8. How much variability in chemical structure is there in individual brand biologics: (1) batch-to-batch, and (2) as a result of manufacturing changes? What are the implications, if any, for FOBs testing requirements, naming, and interchangeability?

9. Should human clinical trials be mandated by statute for all FOBs or should FDA be given discretion whether such trials are needed on a case-by-case basis? Would not requiring human clinical studies of FOBs result in these products having a more difficult time reaching market acceptance? Why or why not?

10. What studies have been required for past approvals of protein products under section 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA)? Have any been approved without clinical trials?

11. Omnitrope is approved in the U.S. (albeit as a 505(b)(2)) and in Europe (as the first biosimilar).

    a. Have patients experienced any problems?

    b. Have patients been switched to Omnitrope from other recombinant human growth hormone products?

    c. If the answer to part b is yes, how are payers handling the availability of this comparable product?

Regulatory/Administrative

1. Some believe Section 505 of the FFDCA provides a regulatory pathway for approval of biosimilars for reference products approved under Section 505. Should a newly created biosimilar regulatory approval process include all biologics approved under the FFDCA as well as those regulated under the Public Health Service Act?

2. The current statute gives FDA discretion to decide whether a change in an approved biologic requires assessment through a clinical trial. Do you think this statutory discretion has been appropriate or adequate? What has been its effect on patient safety?

3. What FDA office should review FOBs?

4. What standards are required to assure sufficient similarity between the FOB and the reference product? Is the requirement that the FOB be "highly similar" to the reference adequate or should an applicant be required to establish that the FOB is "as similar as scientifically as possible"? How would FDA assess these requirements?

5. Should FDA be required to promulgate regulations and guidance before reviewing applications? Why or why not? Furthermore, should FDA be required to issue and permit public comment on product-specific guidance before submission of applications?

What are the advantages and disadvantages? How long will it take to put a regulatory framework in place, including new regulations and guidances for FOBs?

6. How much in additional appropriations or user fees would FDA need to implement a generic biologics program? What proportion of resources should come from user fees? How would that relate to the user fees that are assessed for traditional drugs and/or biologics?

Interchangeability

1. Does current science permit an assessment of interchangeability (substitutability) for any biologics at this time? What is the likelihood that interchangeability assessments for some or all biologics will be possible in the future, and in what period?

2. In general terms, what types of testing or data would be necessary to establish that two biologics are interchangeable?

3. How should product-specific requirements for demonstrating interchangeability be established? Should the statute prohibit interchangeability assessments or give FDA the authority to determine interchangeability as science permits? Please explain your answer.

4. Should there be product specific guidances, with opportunity for public comment, on establishing interchangeability before submission of applications? What are the advantages and disadvantages?

5. What are the potential risks to patients from interchangeability of one biologic for another? If FDA finds two biologics interchangeable, should physicians, pharmacists, and patients feel comfortable with substitution by pharmacists? Why or why not? How would interchangeability affect patient access to biologics?

6. How would interchangeability affect competition in the market place, and/or reimbursement by health plans? Will it affect the costs of biopharmaceuticals?

Patents

1. In your view, how long is the current effective patent term for pharmaceuticals? Specifically, how long on average are drugs marketed under patent protection following FDA approval?

2. The Hatch/Waxman Act restored innovator patents up to 14 years, and further provided manufacturers with 5 years of data exclusivity. Is this a good model for biologic

manufacturers? What lessons can we learn from the Hatch-Waxman Act, and apply towards Congress's discussion about FOBs?

3. Please explain if patents on biotech medicines will provide meaningful protection of intellectual property if a pathway is created to allow for the regulatory approval of FOBs? How do patents on biotechnological medicines compare or differ in the value they offer to traditional small-molecule drugs, if an FOB's pathway requires only that the FOB be highly similar to the reference product?

4. What procedures, if any, should be included in legislation to enable reference product companies or third parties to identify potential patent infringement claims by a biosimilar company and to ensure timely resolution of legal disputes?
5. If patent issues are to be addressed in a statute, how should we balance the interests of third-party patent holders and the reference product sponsor?

6. Should an FOB statute require FDA to administer patent listing and notification provisions as Hatch-Waxman does? Has this process been an appropriate and efficient use of FDA's resources and expertise? Why or why not? Can appropriate notification be accomplished through an alternative process that does not enlist FDA resources?

Incentives/Exclusivity/Investment

1. Should reference product manufacturers be given a period of exclusive marketing in addition to the patent-term restoration already provided to them under Hatch-Waxman? If yes, how much is necessary to provide adequate incentives for innovation without unnecessarily delaying competition?

2. What types of assessments have been conducted to determine the minimum term of exclusivity that will enable a robust industry for discovery and development of biologics?

3. How should exclusivity for modifications to approved products be addressed?

4. What benefits do innovator firms obtain from data exclusivity, and how is this protection different from patent protection?

5. Do you think biologics should receive a different period of data exclusivity than drugs? Why or why not?

6. What policy considerations justify that patent protections be the principal form of intellectual property protection for biologics and drugs?

7. If a follow-on biologics pathway was created without additional incentives—beyond existing patent protections—for continued innovation, how would innovation be affected either positively or negatively? What additional incentives, if any, would be necessary to support continued research and innovation, including at American universities?

Economic Impact

1. How much savings would a generic biologics pathway create and in what period (taking into account the time it will take to implement any new law, and the time needed by manufacturers to develop products and submit applications)? Please describe the evidence on which you base your answer.

2. Can you provide an estimate of the amount of money your agency/company will spend on biological products over the next 10 years, in absolute dollars, and as a percentage of total program/plan spending? If FOBs, approved by FDA as comparable to the brand name product, were available, what is your estimate for the cost of the reference product and the follow-on product?

3. What implications would a follow-on biologics pathway have on U.S. economic competitiveness and leadership in protection of intellectual property rights?

4. What implications does the treatment of patents in the context of a follow-on biologics approval pathway have for the future of biotechnological innovation?

5. If a follow-on biologics pathway was created without ample incentives for innovators to continue to innovate, what would the effect be for future research, current clinical programs, and universities?

European Model (abbreviated approval pathway)

1. The European Union (EU) regulatory system for biosimilars requires the development of product-specific guidances which detail the standard for approval that would need to be met by a biosimilar in a defined product class. Do you think these guidances would provide similar benefits to industry, healthcare providers, and patients in the U.S.?

2. Legislation passed by the European Parliament encourages innovation by providing 10 years of market exclusivity, extendable to 11 years for select new indications of use, for innovator biologics, thereby preventing the introduction of FOBs during that period. Should the U.S. be guided by treatment of drugs and biologics in the EU with respect to exclusivity periods?

3. If the U.S. adopts incentives for innovation in biologics that are substantially less than those afforded in Europe, what could the potential effect be on U.S. competitiveness?

4. To what extent do you agree or disagree with the EU's current model when it comes to access to needed biologics, patent protection, patient safety considerations (including interchangeability), and the length of time needed for the approval of a new product? What are the advantages and disadvantages of the EU's model? Are there other models that the U.S. can examine? If yes, what are the strengths and weaknesses of their models?

5. FOBs are now approved in Europe, and FDA has approved a number of follow-on protein products under the FFDCA. Have these shown any problems with respect to safety or efficacy? In what ways are these different from any safety problems seen with brand products?