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May 2, 2008

The Honorable Frank Pallone
Chair, Health Subcommittee
2125 Rayburn House Office Building
Washington, DC 20515-6115

The Honorable Nathan Deal
Ranking Member, Health Subcommittee
2125 Rayburn House Office Building
Washington, DC 20515-6115

Re: American Society of Clinical Oncology Responses to House Energy & Commerce Committee Question on Generic Biologics Legislation

Dear Chairman Pallone and Ranking Member Deal:

The American Society of Clinical Oncology (ASCO) is the leading medical society for physicians involved in cancer research and treatment with more than 25,000 members worldwide. We appreciate the opportunity to comment on these important questions to the House Energy & Commerce Committee's consideration of legislation to establish a pathway for the approval of generic versions of biologic therapies.

We have provided below answers to the questions for which we have a position or principles. In addition, attached to this letter is a statement of principles that our Board of Directors has approved.

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?

   We encourage the committee to review the "Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins" developed by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP). The document is available on the internet at http://www.emea.europa.eu/pdfs/human/biosimilar/1432706en.pdf.

   Based on that document, ASCO suggests the following answers: Immunogenicity to a biotechnology-derived therapeutic protein is an unwanted response by the patient's immune system. The effects could range from no clinically significant symptoms or signs to severe and life-threatening conditions, in addition to reducing the clinical efficacy of the therapeutic protein. The triggers for these adverse responses are multi-factorial and can be related to the patient, their disease or to the therapeutic protein. Therefore, the immunogenicity potential for a therapeutic protein should be considered on an individual basis, as there is little ability to extrapolate immunogenicity-potential from a related protein, unless fully-justified scientifically. It is important to note that biological therapy (protein-based) always carries a higher risk of immunogenicity than standard chemical therapy, nothwistanding similar formulation/excipients.
   For further description of differences between small molecules and therapeutic proteins, please see the following editorial published in the International Journal

2008 Annual Meeting
May 30–June 3, 2008
Chicago, Illinois

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of Artificial Organs: http://www.artificial-organs.com/content/248/2549/8713.pdf.

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 Drug Administration (FDA) be given discretion to determine whether such studies, and what types of studies, are needed on a case- by-case basis?

   Clinical trials to assess immunogenicity in biogenerics would be necessary in most, if not all, cases. FDA should be given substantial discretion in forging the regulatory pathway for approval of individual classes of biogeneric products, including determination of whether 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?

   FDA should be given the discretion to determine whether such testing is necessary. FDA should provide general considerations in guidance on immunogenicity, in addition to addressing this topic in each class or product-specific guidance issued by the agency.

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?

   FDA should be given the discretion to make this determination scientifically. Extrapolation of efficacy to other indications should not be assumed by the company. Clinical trials are not necessarily required and in many cases are not needed. However, the rationale for the request to forgo clinical trials should be justified scientifically.

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?

   Every biogeneric product should be subject to meaningful post-marketing safety surveillance which should include a robust plan for adverse event reporting. Special considerations should be made to track patients who cross-over from the innovator product to the biosimilar.

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?

   The main issue is the ability to trace an adverse event back to the actual drug that was given. If substitutions are allowed at the pharmacist level and the non-proprietary names are the same, then it will be very difficult to trace an adverse event back to the actual drug taken received by the patient and its manufacturer. The physician will also not know what drug was actually given to the patient. Today's biologic therapies for cancer are largely IV indications

given to a patient through a dispensing physician in an office setting. Nevertheless, this same concern about substitution applies.

Currently, the United States Adopted Names (USAN) council works closely with the World Health Organization (WHO) International Non-proprietary Name (INN) expert group to reach consensus on generic names as appropriate. Decisions made regarding the use of non-proprietary names should be a global consensus agreement of key stakeholders to ensure world-wide traceability of adverse events to a specific drug/drug manufacturer.

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?

   If the mechanism of action of the innovator product is known, then the FOB must have the same mechanism of action. If the mechanism of action is not known then it is not reasonable to require this of the FOB. However, clinical studies will be particularly important in these circumstances to establish similar safety and efficacy to the innovator product.

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?

   Determination of these specifications should be left to FDA. FDA should be required to set standards in product and class-specific guidance.

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?

   Clinical trials to demonstrate sufficiently similar safety, efficacy and immunogenicity in biogenerics would be necessary in most, if not all, cases. FDA should be given the discretion to determine what data is needed to show that the innovator and FOB are similar. These data requirements should be adequately described in guidance, which has been reviewed by the public and finalized by the agency before approving any FOBs.

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?

    ASCO has no comment.

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?

ASCO has no comment.

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?

   ASCO has no comment.

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?

   FDA should continue to have the discretion to decide whether a change in an approved biologic requires assessment through a clinical trial.

3. What FDA office should review FOBs?

   Biogeneric products should be subject to initial review and oversight post-approval by the Office to which the original innovator product is assigned, rather than a separate "generics" Office.

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?

   Biosimilar should be defined in statute to the extent that it does not impede evolving science. Similarity should be defined more specifically in FDA regulations and guidance documents should set more specific criteria for a particular product class. That being said consideration should be given to the following: biosimilars should be shown through analytical, animal and clinical studies as appropriate to be highly similar to the reference product, using the same mechanism of action if known (excluding minor differences of inactive components). Biosimilars should use the same route of administration, dosage form and strength as the innovator product with no clinically meaningful differences in safety, efficacy and immunogenicity. The manufacturer of the biosimilar product must meet similar manufacturing and inspection standards as the manufacturer of the innovator product.

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?

   Guidance documents—either on a class-specific basis or in some cases on a product-specific basis—should be published to ensure consistency of standards and predictability of regulatory

action. The public should be given the opportunity to comment on these guidance documents before they are finalized.

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?

   Congress should ensure that FDA is provided adequate resources to meet the new demands of assessing bioequivalence in the number of biogeneric products that will be presented to the agency once standards are in place. ASCO believes some combination of user fees and appropriated funds is appropriate, consistent with current funding for application review.

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?

   The current science, if a product was established to be similar in safety, efficacy and immunogenicity, does support interchangeability. However, even if the decision is made to use the same non-proprietary name, the two products cannot be established as identical. And therefore it is important that thought is given to the management of adverse event reporting. For the purposes of traceability for drug safety issues, consideration should be made as to how FOBs would be distinguished from the innovator in the case of adverse event reporting.

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

   Interchangeability should be determined only through clinical trials adequate to support substitution of the biogeneric product for the innovator product without sacrificing safety or efficacy. .

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.

   FDA should be given the regulatory authority to determine interchangeability. However, prior to reviewing FOB applications, FDA should put forth guidance on general FOB topics, topics specific to that class of biologics and where major differences occur in-class, product-specific guidance should be developed prior to approving interchangeable FOBs. Guidance documents should be subject to public comment before being finalized.

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?

   See answer above #3

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?

   No system should be adopted that would limit physician choice among "biosimilar" products or require substitution of products that have been designated "interchangeable." In every instance, the physician should decide which among similar products should be prescribed. If a pharmacist performs a substitution, the physician will not know what product was actually received by their patient. Today's biologic therapies for cancer are largely IV indications given to a patient through a dispensing physician in an office setting. Nevertheless, this same concern about substitution applies. The ability to properly report adverse events by product and trace that product back to the manufacturer is imperative to ensuring proper post-marketing safety reviews of FOBs and innovator products.

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

   ASCO has no comment.

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?

   ASCO has no comment.

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?

   ASCO has no comment.

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?

   ASCO has no comment.

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?

   ASCO has no comment.

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?

   ASCO has no comment.

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?

   ASCO has no comment.

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?

   Non-patent data exclusivity should be adequate to ensure continued innovation, both in new products and in new indications for existing products. Additional years of exclusivity should be provided as an incentive to development of new indications. ASCO does not have a position on a specific number of years.

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?

   ASCO has no comment.

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

   ASCO has no comment.

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

   ASCO has no comment.

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

   ASCO has no comment.

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

   ASCO has no comment.

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?

   ASCO has no comment.

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.

   ASCO has no comment.

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?

   ASCO has no comment.

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

   ASCO has no comment.

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?

   ASCO has no comment.

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?

   Without ample incentives, research and development involving the innovator product will halt.

European Model (abbreviated approval pathway)

1. The European Union (EU) regulatory system for biosimilars requires the development of product-specific guidance 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.?

Yes. FDA should be required to develop product-specific guidance and allow public comment prior to reviewing FOB applications in that product class. FDA should also develop overarching biosimilar regulations, and more general non-clinical, clinical and Chemistry, Manufacturing and Controls (CMC) guidance documents similar to the EU guideline structure.

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?

   ASCO has no comment.

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?

   ASCO has no comment.

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?

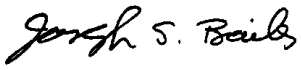
   ASCO has no comment.

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?

   ASCO has no comment.

Thank you for the opportunity to comment on this important issue. Please do not hesitate to contact us with any questions.

Sincerely,



Joseph S. Bailes, MD
Chair, ASCO Government Relations Council