



May 2, 2008

The Honorable Frank Pallone, Jr., Chairman  
Energy and Commerce Health Subcommittee  
U.S. House of Representatives  
Washington, DC 20515

The Honorable Nathan Deal, Rank Member  
Energy and Commerce Health Subcommittee  
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Dear Mr. Chairman and Mr. Deal:

The National Organization for Rare Disorders, Inc. (NORD) thanks you for the opportunity to respond, in part, to questions posed about the creation of a regulatory pathway to the approval of follow-on biologics (FOBs). We agree that safe and efficacious FOBs have the potential to lower the cost to patients and the healthcare system, improve access, and stimulate innovation of new and potentially life-saving therapies.

In consultation with leading economic, regulatory, legal, and government experts in the field, NORD has developed a core set of principles we believe are critical to the development of any regulatory pathway to FOB therapies:

- Ensure that a patient's safety and therapeutic outcome does not differ from those of the innovator product.
- Provide fair exclusivity to innovator and FOB manufacturers.
- Establish an unambiguous and transparent regulatory pathway that will encourage competition, stimulate innovation, and provide patients access to biologics that cost less.
- Allow the Food and Drug Administration (FDA) the flexibility and authority to determine on a case-by-case basis what data it needs to approve FOBs. The agency must have an unobstructed framework to use its scientific expertise to approve safe, pure and potent FOBs.
- Decouple litigation between the innovator and FOB manufacturer and the review and approval of the FOB application at the FDA.
- Provide a clear and timely resolution to patent disputes and prohibit frivolous suits that restrict access to FOBs and delay competition in the marketplace.
- Ensure predictability for scientifically proven, safe, and effective FOBs into the marketplace.
- Ensure that the seven years of exclusivity provided by the *Orphan Drug Act* continues to encourage the development of new, life-saving drugs and biologics for the treatment of rare diseases. We do not agree, at this time, that "ultra-orphans" should receive additional exclusivity. Should this issue need to be addressed in the future, NORD will be pleased to work with the Committee.

NORD does not profess to have the expertise necessary to answer the majority of questions. However, in 2003, NORD sought to determine whether FOBs were scientifically feasible and desirable, and called upon experts to address scientific and economic questions in the first national meeting held on FOBs (please see the meeting summary enclosed). NORD recently sought additional advice from experts in preparing responses to the questionnaire. These are reflected in our responses to many of the questions posed in Section I (Science/Safety) and to all of the questions posed in Section II (Regulatory/Administrative).

## **Section I. Science/Safety**

### **Question 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?**

Immunogenicity is defined as the ability of an antigen or vaccine to stimulate an immune response. In rare cases, hypersensitivity to a biologic may cause shock, rash, asthma or an autoimmune response after administration. Immunogenicity risks may vary according to the type of biologic. For instance, FOB antibodies will not be identical to the innovator product in terms of antigen-recognizing variable (V region) sequences and glycosylation, and these differences can lead to immunogenicity.

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

Immunologic reactions to biologics are usually rare and detection of small levels of risk requires statistically adequate methods. Because immunogenicity can not be predicted, the question arises, "What is sufficient testing to ensure that patients are safe?" That is a question that can only be answered when comparing the innovator and FOB in pre-clinical trials. The FDA should be given the regulatory authority to make the final decision regarding whether, and what types of immunogenicity testing and studies are needed. It should be noted that the same standards should apply to both the innovator and FOB.

### **Question 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 have discretion regarding both questions. The general questions in current legislative proposals relate to equivalence (sufficient similarity) and there are two of these: comparability and interchangeability. The focus of the two questions is on pharmaceutical equivalence, particularly whether the active moiety(ies) in the FOB are equivalent to the innovator product. This is because most biologics are given as solutions and thus demonstration of bioequivalence should usually not be necessary, barring important excipient differences for certain parenteral products. This question can be answered by a variety of means up to and including limited clinical trials. The totality of the evidence should be compelling, and the evidence based on physicochemical, biologic, potency, non-clinical and clinical studies, coupled with post-marketing surveillance, as needed. FDA may decide that there does not need to be a reliance on comparative clinical trials for all indications, although sometimes that might be necessary for highly pluripotent therapeutics with markedly different indications (such as antiviral and anticancer).

**Question 5. Under the FDA 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 difference from those that have been required and/or requested for the reference product?**

Title IX of the FDAAA gives the FDA increased authorities to required Phase IV studies and/or post-marketing surveillance. As required by law, the same standards should apply to both the innovator and FOB.

**Question 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 have the same one? Why or why not?**

The innovator and FOB should have the same mechanism of action, which is a fundamental element of pharmaceutical equivalence. The principle of substitution is based on the understanding that one active moiety with the same mechanism of action is being substituted for another active moiety with the same mechanism of action. The innovator manufacturer has the responsibility of determining the mechanism of action, not the FOB manufacturer. The FOB needs to show pharmaceutical equivalence and, if necessary, bioequivalence, for market access. The goal of substitution is to assure that the innovator and FOB have the same quality attributes will be similar, such as therapeutic outcomes.

**Question 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?**

Human clinical trials should not be mandated by statute for all FOBs. Congress should grant FDA the authority to determine whether human clinical trials of FOBs are required to assure either comparability or interchangeability. Acceptance of FOBs by the healthcare and patient communities should be based on the FDA's scientific and regulatory expertise in making judgments about comparability and interchangeability.

## **Section II. Regulatory/Administrative**

**Question 1. Some believe Section 505 of the FDCA 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 FDCA as well as those regulated under the Public Health Service Act?**

Yes, but in a novel way. We urge Congress to consider amending the definition of biological products in Section 351 of the Public Health Services Act (PHSA), such that all therapeutic proteins and related products generally considered as candidates for FOBs would be subject to regulation solely under the FDCA and no longer under the PHSA, excluding gene therapy and cellular and tissue-based therapies.

Section 505 has been used as an approval pathway for biologics that are similar to reference proteins already approved under the FDCA. Both FDCA §§ 505 (j) and 505(b)(2) provide pathways that permit reliance on previous findings of safety and effectiveness for previously approved drugs under the FDCA. However, the increased structural complexity of biologics makes it unlikely the 505(j) pathway, which requires that the subject drug be shown to be the same as the reference drug, will be effective even for FOB (relatively simple) proteins originally approved under §505.

The 505(b)(2) pathway provides FDA greater flexibility, permitting data reliance in proportion to the degree of similarity between products (as opposed to the all or nothing reliance on a 505(j) application), and was recently used to obtain approval for Omnitrope®. The biologics currently regulated under Section 505 are only a small percentage of all biologics, are all relatively simple, and can all be subject to 505(b)(2) applications. Biologics currently approved under the PHSa encompass a greater degree of complexity, spanning the gap from simple proteins to complex gene therapy, and while the majority of these are amendable to regulation under the FDCA, both gene therapies as well as cellular and tissue-based therapies would remain under the PHSa. Thus, not only is it not necessary to include biologics currently approved under FDCA Section 505 in any new follow-on biologics legislation, but the current 505(b)(2) process could actually function as the regulating system for review and approval of FOBs – giving FDA discretion to rely on the previously approved product to the degree that current science warrants.

**Question 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?**

While the current system has not caught every deleterious change to a biologic, such as the change in the stopper in Johnson & Johnson's Procrit®, there does not appear to be any authority better equipped than the FDA to determine whether changes necessitate a new clinical trial. Statutory language that sets forth criteria for when clinical trials are/are not warranted will become outdated quickly with rapid advances in biological science. The system, while not perfect, is likely optimal as is.

**Question 3. What FDA office should review FOBs?**

The question is whether FOBs should be reviewed in the same division that reviewed the initial biologic, or in a separate FOB unit. Provided an appropriate incentive for timely review is included, we suggest that review should occur in a new Office of Biosimilars. The creation of a new Office of Biosimilars may focus resources, and a separate office dedicated to these products may be the best way to make certain that these FOBs receive a priority high enough to ensure timely review. However, this office must have the requisite therapeutic area of expertise.

For drug approvals, whether a successor drug is reviewed in the Office of Generic Drugs (OGD) or the same division as the innovator drug, depends on whether the application is a 505(j) or 505(b)(2). A 505(j) application contains only limited data designed to show that a generic drug is identical to the innovator drug. The methods of analysis used to make this determination are common to all drugs, and such characterization is generally adequate to make a determination on similarity. Thus, no therapeutic area of expertise exists in OGD. In the unusual event that more product-specific expertise is demanded (e.g., for a non-systematically active therapy), OGD must consult with the division in charge of approving the innovator drug. A 505(b)(2), in contrast, typically requires consideration of the disease as well as product similarity.

FOBs will most likely be 505(b)(2)-type situation where therapeutic-area specific expertise will virtually, if not always, be needed to assess preclinical or clinical data. A separate Office of Biosimilars is needed and should be staffed with sufficient medical expertise or a mechanism to consult with the Office of New Drugs (OND) divisions. Such a consultation can be achieved. For instance, a new Office of Biosimilars will need to have consultation on vital chemistry and manufacturing issues from the CDER Office of Pharmaceutical Science (OPS) and few think that this can not be done if adequate resources are available in OPS.

However, the concern with consultations from the OND divisions is that, if the OND reviewing division is not sufficiently incentivized to review FOB applications, the applications could languish in a general review division in favor of approval applications with a PDUFA date. Therefore, incentives for timely review must be included in any legislation.

**Question 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 possible”? How would FDA assess these requirements?**

Given the diversity of FOBs, which range from short peptide sequences to longer chains with complex glycosylation, it would be difficult to establish a meaningful similarity standard by statute. Instead, FDA should be given the same flexibility that exists in the 505(b)(2) process to rely on previous data to the extent warranted by the similarity of the products as discerned using the latest characterization method.

**Question 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 guidance for FOBs?**

The response will address regulations and guidances separately.

Because of the attendant delay in waiting for approval of FOBs under an agency-imposed regulatory scheme, the agency should not promulgate regulations before the first application is accepted.

The question asks about two different types of guidance documents: product-specific guidance, detailing why FDA believes are recommended tests and procedures for certain products or classes of products, and general guidances applicable to FOBs as a whole or to large numbers of FOBs.

The first type, guidance applicable to a particular product, should not be produced until FDA has gained experience with FOB applications for the product in question. A lack of official guidance will not prevent companies from individually contacting the FDA to obtain guidance, and in fact forcing this personal interaction will more effectively tailor the tests expected for initial products to up-to-the-minute agency thinking. N.B.: This is consistent with FDA’s issuance of guidance documents in a particular therapeutic area (e.g., rheumatoid arthritis) after approval of products in that area. Such guidance documents are only possible after the agency has gained enough experience in the area to speak in a general manner.

In contrast, issuance of general guidance would probably be more desired by industry before promulgation of the regulations to guide action taken before the regulations become effective. There would be little point to such an exercise, however. Such a guidance, based not on a promulgated regulation but rather directly on a statute, would fall under Executive Order 13422, which amended Executive Order 12866. As the FOB industry could be expected to have an impact of more than \$100 million on the economy, the guidance would be considered a significant guidance document under the Executive Order. Such a classification would require both a comment period and review by OMB.

Given the delay inherent in this process, there is no reason to issue guidance before the promulgation of the regulations. Instead, waiting until the regulations are issued would allow simultaneous release of guidance documents intended to further clarify the requirements, meaning a combined regulatory/guidance scheme could be in place within 3-4 years.

**Question 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?**

Estimates of the total requirement would depend on the expected number of submissions, which we are not in a position to estimate right now. Regarding the percentage of the total that should come from user fees, in FDA's 2006 PDUFA report, user fees comprised 56 percent of operating funds in 2005 and 58 percent in 2006. We see no reason to depart from this approximate percentage.

While smaller fees could be seen as desirable to keep costs down for the eventual consumers of these products, smaller fees would also provide less of an incentive for prompt review and could lead to understaffing in the division.

Also, as mentioned before, if review of FOBs occurs under the FDCA, user fees and goal dates have already been established and would apply to FOB products.

If costs remain a concern, rather than focus on the overall percentage, it might be preferable to include some sort of tiered user fee system. This could depend on the level of complexity of the application, with higher fees corresponding to applications requiring additional studies or other information necessitating a more lengthy review, and lower fees for those that are less complex and would require review of fewer studies.

**Summary**

Increased access to therapies that are safe, pure and potent, and lower in cost, is important to NORD and the entire rare disease community. It is the hope of millions of men, women and children affected by rare diseases who do not have a treatment specific to their disease, that competition will spur the development of newer and more effective medicines.

NORD thanks you for the opportunity to respond to your questions, and we welcome the opportunity to continue to work with the entire Committee to craft legislation that will benefit all stakeholders. Please contact Diane Dorman at (202) 496-1296 or [ddorman@rarediseases.org](mailto:ddorman@rarediseases.org) for more information.

Sincerely,

/s/ Peter Saltonstall

Peter Saltonstall, President

Cc: The Honorable John D. Dingell, Chairman  
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The Honorable Joe Barton, Ranking Member  
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