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RE: DOCKET NO.: 2004N-0355

Schering Plough welcomes the opportunity to comment on the Federal Register notice entitled, "Scientific Considerations Related to Developing Follow-On Proteins." We thank FDA for bringing this important issue into the public domain for consideration of the many scientific issues affecting the development of follow-on proteins. As such, Schering-Plough supports the comprehensive comments submitted by the Pharmaceutical Research and Manufacturers Association (PhRMA) detailing the scientific and regulatory challenges facing the possible introduction of follow-on proteins. We will not reiterate PhRMA's comments in order to provide additional information we believe relevant to FDA's consideration of standards for quality, safety and efficacy of certain follow-on proteins.

During the public workshop held on September 14 and 15, 2004, FDA requested sponsors to provide data, when available, supporting the development requirements recommended for follow-on proteins.

Because of the inherent variability associated with protein therapeutics, Schering-Plough encourages the FDA to establish a case-by-case approach to establishing the regulatory standards to be applied to follow-on protein therapeutics. The case-by-case approach is essential to ensure that patients are not exposed to unanticipated risks of reduced safety or efficacy if administered a follow-on protein therapeutic which was approved through an abbreviated process. In the public discourse regarding follow-on proteins, the currently approved interferon therapeutics have often been mentioned as if they represent a single class of products with identical issues of safety and efficacy.

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Case-by-Case Assessment Required

Schering-Plough believes that each interferon type (alpha2a, alpha2b, beta, gamma, and consensus) represents unique regulatory issues due to differences in the manufacturing processes, the variability of the glycoprotein, the resulting specific activity, formulation which could contribute to immunogenicity and differences in the indications of use, the severity of the patient populations, and the duration of therapy. Each of these factors impacts the types of specific requirements for developing follow-on proteins.

Schellekens and Ryff [1] define a system in which protein products should be considered case-by-case based on factors such as structure/function relationship, differences in patient population, and immunological response.

Under this categorization, the majority of follow-on proteins would necessitate a full dossier as required for an NCE, including full details of the gene and expression vector, the expression system including full descriptions of the master and working cell banks, fermentation or culture process, purification process, formulation, fill, finish, storage and shipping processes, cleaning and shipping validation studies, physico-chemical and biological characterization for the purified product, analytical methods and their validations, stability data on drug substance and drug product, standard pharmacological and toxicology data, *and sufficient clinical data to demonstrate clinical equivalence* to the innovator product for a registered indication indicative for both efficacy and safety.

Only when the patient population is representative for safety and efficacy can the clinical data be extrapolated to a different indication in a similar population. Population differences in immunological responses which may exist due to factors such as: disease type and/or severity, gender, and geographic origin would preclude such extrapolation. Safety considerations would necessitate separate clinical trials for indications that differed in the characteristics of the patient population.

Immunogenicity and Clinical Relevance

For follow-on biologics known to be associated with possible immunogenicity, the clinical trials should be powered to detect clinically significant differences and sufficiently sized to make a comparison in product immunogenicity. As shown in **Table 1**, a variety of clinical consequences have been reported as a result of the development of an immune response to innovator recombinant therapeutics.

Schellekens and Ryff [1] recognize this observation and suggest that immunogenicity and its impact on patient safety and effectiveness should be an included focus. For products that induce antibodies that can neutralize important host factors and potentially lead to serious problems, immunogenicity testing should be included in both the Phase III registration trial and as part of Phase IV commitments for post-marketing.

Table 1. Reported clinical consequences of immunogenicity. [2]

| <i>Recombinant Protein</i> | <i>Reported Consequence of Antibodies</i> |
|-----------------------------------|--|
| Growth hormone | Decreased activity |
| Insulin | Resistance |
| Erythropoietin | Red cell aplasia |
| Factor VIII | Decreased activity |
| Interferon alpha | Decreased activity |
| Interferon beta | Decreased activity |
| CD3 MAb | Increased CD3 |

It is well understood that formation of antibodies, and in particular, neutralizing antibodies, against interferon alpha is a complex process. The nature and immune modulatory activity of interferon and other cytokines themselves may be directly involved. The implications are that in some indications or disease states some strongly immunogenic cell type interacts with certain cytokines, including interferon alpha.

Schering-Plough and others [4, 5, 6, and 7] have found that the following factors influence antigenicity for human Interferon alpha as well as other therapeutic recombinant proteins:

- Route, dose, frequency, and duration of administration
- Assays
- Type of IFN and chemical structure, including amino acid sequence, glycosylation and pegylation
- Contaminants and impurities
- Formulation and stability, physical and chemical degradation such as oxidation [8, 9] or aggregation
- Type of disease/indication
- Genetic background of patient, and
- Unknown factors, which could include associated diseases and concomitant therapy.

The rates of binding and neutralizing antibodies are different for different indications of interferon alpha2a (Table 2), the consequences of immunogenicity may also differ. These clinical consequences can include [2]:

- No effect
- Reduced efficacy
- Enhanced efficacy
- Neutralization of natural protein
- General effects of antigen-antibody complexes

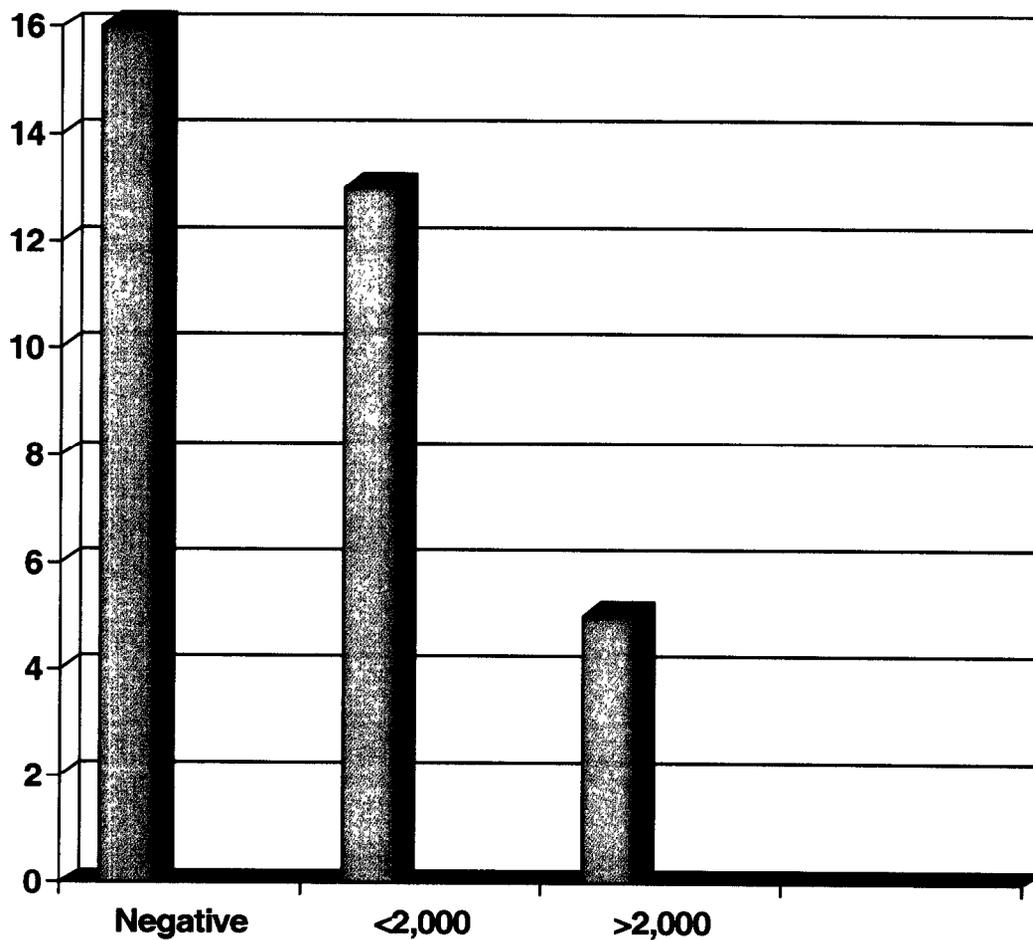
Table 2. Type of disease and antigenicity of Interferon alpha.

| | <i>Binding Antibodies (%)</i> | <i>Neutralizing Antibodies (%)</i> | <i>Neutralizing Antibodies (%)</i> |
|-----------------------|--|---|---|
| <i>Disease</i> | Interferon alpha2a | | Interferon alpha2b |
| Renal cell carcinoma | 5.2 | 3.4 | NA |
| Melanoma | 13.7 | 9.8 | <3% |
| CTCL | 25 | 25 | NA |
| CML | 17.6 | - | NA |
| Chronic HBV | 16.8 | 14.6 | 13 |
| Chronic HCV | 55 | 38.5 | 7 |
| Genital warts | 67.7 | 53.4 | 0.8 |
| Kaposi's sarcoma | | | 4 |

For interferon alpha2a, a reduction in efficacy has been reported. For patients with hepatitis C, a correlation has been observed between disease relapse and anti-interferon antibodies (Table 3 and Figure 1). We want to stress that for this type of molecule pre-approval immunogenicity assessment is essential [3]. It is also important to recognize that the population and indication dependence of the immunogenicity limits the extrapolation of data.

Table 3. Relation between relapse and anti-interferon antibodies in HCV patients.

| <i>Population</i> | <i>Antibodies (%)</i> |
|-------------------|-----------------------|
| Overall | 40 |
| Relapse patients | 89 |

Figure 1. Relationship between Sustained Response and Antibody Level in Interferon alpha2a-treated HCV Patients.

Predictions from Preclinical Models

Today, there are no established preclinical models that can be substituted for the information gained from human clinical trials to evaluate immunogenicity. There have been preclinical models which have attempted to determine how interferons may lead to a break in immune tolerance. For example, Braun et al [4] studied recombinant human interferon alpha2 in transgenic mice tolerant for human interferon alpha2. To mimic the immune modulatory activity of the human interferon alpha2, they injected both the recombinant human interferon alpha2 with either the recombinant murine interferon alpha2 or polyIC, an interferon inducer. The concurrent treatment did not break the tolerance toward the interferon alpha2 monomers. This animal model did not model a specific disease state and does not reflect clinical data.

Note that other preclinical studies of recombinant human interferon alpha2 in this transgenic mouse model did demonstrate that aggregates of recombinant human interferon alpha2 break tolerance and thus were found to be immunogenic [4]. However, while the model may be useful for gaining insights about the physical states of a follow-on interferon alpha2, clinical data suggest that patient disease state may be a more critical factor for some indications for interferon alpha2. As a result the animal model may be a useful addition to physical characterization of interferon aggregates but, the animal data cannot predict the outcomes that may occur during patient treatment. The degree of aggregation and the mechanism by which aggregates break immune tolerance in humans is unknown. Continued research is required to understand how the results from these animal models may be related to the immune response in humans.

Taken altogether the preclinical and clinical data suggest that preclinical models would likely not be predictive of clinical immunogenicity for a follow-on interferon alpha protein and that clinical trial data is required.

Conclusion

Due to the absence of preclinical methods of predicting the incidence or consequence of protein therapeutics and the significant clinical impact associated with the development of anti-interferon antibodies, the FDA is encouraged to adopt a pre-approval requirement for human clinical data demonstrating indication-specific rates of antibody formation in the regulatory standards for follow-on interferon subtypes. Interferon therapies are used to treat patients with significant life threatening diseases and the development of anti-interferon antibodies has been associated with a reduced clinical benefit. The patient characteristics have a significant impact on the observed rates of immunogenicity and it is unknown how these characteristics may affect the clinical utility of a follow-on interferon.

Based on the evidence provided, Schering-Plough believes a full regulatory dossier must be required for any interferon considering follow-on development. The specific regulatory requirements would include the following [1; 10]:

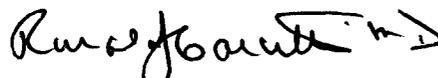
1. Genetic engineering including construct characterization and cell bank characterization;
2. Fermentation in process controls, raw materials, cell line stability, and process validation;
3. Purification in process controls and process validation;
4. Drug product manufacture in process controls and process validation;
5. Drug substance release tests and specifications, method validation, and stability;
6. Drug product release tests and specifications, method validation, and stability;
7. Preclinical toxicology;
8. Preclinical pharmacology with both in vitro and in vivo models;
9. Pharmacokinetics and pharmacodynamics;
10. Controlled clinical trials evaluating safety, efficacy and immunogenicity for each indication

Given the potential safety and efficacy concerns with these products, we do not believe it is appropriate to limit the pre-approval evaluation of interferon products to pharmacokinetic and pharmacodynamic parameters and rely on post-marketing exposure to assess the immunogenicity of these products as suggested during the public workshop. In principle, we accept the limitations of clinical trial designs when considering exposure rates and evidence of rare adverse events. However, we do not believe that patients should be exposed unwittingly to an approved product without a full regulatory and scientific understanding of the product's quality, safety and efficacy.

We would like to thank FDA for this opportunity to comment on this important topic and look forward to further public dialogue on both the scientific and regulatory/statutory implications of follow-on proteins.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j), as well as the FDA Regulations.

Sincerely,



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