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Enclosed, please find the document submitted by Dr. James Green of Biogen Idec for the Docket No. 2004N-0355/Scientific Considerations Related to Developing Follow-Biologics Protein Products.

Thank you for your assistance!

Kind Regards,

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FINAL

Commentary on "Follow-on" Biologics: Considerations for Minimum Data Sets to Support Registration, James D. Green, Ph.D., DABT

Reaching regulatory agreement on data requirements to support the registration of "follow-on" Biologics in the US has not yet been achieved; although the FDA has initiated significant activity in this area (1,2). In Europe, regulatory authorities have already adopted a "case by case" approach and have communicated their considerations in a well-written guidance that provides direction and enumerates appropriate considerations (3). The directive recognizes that a "product claimed to be similar to another one already marketed" will require an extensive product comparability exercise. Furthermore, it is clearly acknowledged that biochemical analyses of the drug substance/product are not sufficient to address all aspects of quality, safety and efficacy. Preclinical and clinical bridging studies are needed; the extent and scope of these studies to be determined based on data submitted and the individual circumstances (see Ref. 3, section 3.0). The document concludes by clearly recognizing that in "cases where satisfactory comparability may not be demonstrable, a full preclinical and clinical data package will be required " (see Ref. 3, section 4.0.).

It is well recognized that the development of biologic therapeutics presents unique scientific challenges to preclinical and clinical scientists who are responsible for determining "safe use conditions" and "efficacy" (4,5). However, using the "comparability" approach referred to above, one could envision the evolution of an

"extensive" product comparability data set. Below, I would like to offer additional considerations regarding how a data set such as this might be constructed.

First, to briefly review, a "Product Technical Assessment Program" consists of the following key elements: 1) biochemical characterization studies to confirm structural identity; 2) biological activity studies to confirm potency and maintenance of mechanism of action (MOA); 3) pharmacokinetic studies to confirm that dosimetry remains unchanged; 4) toxicology studies to confirm that the therapeutic ratio and safety profile remains unchanged; and 5) clinical trials that confirm pharmacokinetics, pharmacodynamics, safety, and efficacy.

One might be tempted to conclude that if the "follow-on" product is shown to possess the same physico-chemical characteristics and is shown to be bioequivalent against certain pre-determined pharmacokinetic parameters (i.e., a head to head comparison of the follow-on product to an innovators product), it can be presumed to have the same clinical safety and efficacy profile as the originator's product for the purpose of its approval. Although this approach works well for small chemical molecules with defined characteristics, this conclusion would be erroneous for biologics. There are many examples where process changes were made and unintended consequences to the activity of the product were observed. These examples, which include antibodies, proteins, and fusion proteins, showed unexpected changes in pharmacokinetics, pharmacodynamics, therapeutic index, and immunogenicity rate. These examples highlight the fact that it remains difficult to predict with certainty whether a detected product change will be important or not. It is because of this uncertainty, that all

elements of the "Product Technical Assessment Program" are viewed as essential for the assessment of the integrity, safety and biologic activity of a biologic.

As previously discussed (4), it is now recognized by potential follow-on biologic manufacturers and regulatory authorities that the approach currently accepted for generic small molecules is not appropriate as a path forward for "follow-on" biologics. The path forward at this point in time can only be driven by data and clearly stated data requirements, product experience and an understanding of a product's complexity. The key elements of a "Product Technical Assessment Program" can be used to guide the development of a data set that could be considered sufficient to support the regulatory authorization of a "generic" or "follow-on" biologic. The approach would require head to head comparisons of the "follow-on" product to an innovators product. An example of such a comparison is shown in Table 1.

Table 1: Extensive Product Technical Assessment Program

Study Type	Required Comparison	Probability of Success/comments*
Biochemical	Statistical equivalency on measured parameters and acceptable ranges. (innovator vs. follow-on)	Low-Moderate/ sample 10-12 lots from different geographic regions for comparison to 10-12 follow-on batches, data collected over multi-year period.
Bioassay	Statistical equivalency on measured parameters (innovator vs. follow-on)	Moderate-High/ assay format need not be identical to innovator. Format based on current SOA technology; sample strategy as above. Assay format should reflect an important biologic endpoint. Equivalent performance in a relevant animal model of disease should be demonstrated if possible.
Pharmacokinetic	Statistical equivalency on all disposition parameters (innovator vs. follow-on)	Moderate-high/ dependent on similarity of biochemical, bioactivity profile and process profiles.
Toxicology	14-28 day repeat-dose study at 1x, 5x and 25x the therapeutic dose in one pharmacologically responsive specie; (innovator vs. follow-on)	Moderate/ no toxicologically meaningful differences in safety profiles; qualitatively similar comparison of relative immunogenicity profiles required.
Clinical	Single-dose PK bioequivalence; Example: For multi-dose chronic use products, repeat-dose safety and efficacy; minimum of 6 months immunogenicity and safety assessment (innovator vs. follow-on)	Moderate-High/ assuming above comparisons are met, need to demonstrate no clinically significant differences in safety and bioactivity profile; immunogenicity profile is qualitatively and quantitatively similar; validated surrogate markers may be used to support efficacy. Patient numbers and clinical design requirements are product specific but must be powered to detect differences in safety and efficacy. Phase IV monitoring required.

* SOA: state of art. Above example assumes chronic use; dosing schedule to be matched in toxicology studies. Scope of toxicology studies designed in consideration of product profile.

The "follow-on" manufacturer would be expected to provide a complete Chemical, Manufacturing and Control(CMC) dossier on their manufacturing process. This CMC dossier would be expected to reflect current state of the art requirements (ICH, GMP, batch numbers, etc...). Based on the CMC data and the data set generated as specified in Table 1, conclusions regarding comparative safety and efficacy could be made. Furthermore, it might be possible to further modify the data set required based on unique "case by case" considerations related to: 1) product quality and complexity; 2) the disease to be treated; 3) product-specific clinical pharmacology/toxicology issues; and 4) product-specific clinical trial design issues. Based on the type and degree of differences detected between the "follow-on" product and the innovator's product, the overall profile should raise or lower the level of concern regarding conclusions that can be made.

The approach specified above is rigorous and the requirements are challenging to meet. The fact that the "follow-on" manufacturer is starting with a new cell line and process steps, assays and reagents that are unique to their own product and facility raises, in my view, a high probability that numerous differences between the two products will be detected in 'head to head' comparisons. In a tiered approach, however, these potential differences can be enumerated and assessed as to their likely impact on safety and biologic activity relative to the marketed product(s) and their conditions of administration. In certain instances, the data set could support the conclusion that despite starting with a new cell line and unique process, the data set in aggregate proves the products to exhibit similar safety, dosimetry and clinical efficacy profiles. These data, combined with an appropriate Phase IV monitoring strategy to assess safety, could be adequate to protect and assure patient safety. In other instances, however, the aggregate

number of differences detected during the various stages of the tiered assessment may raise concerns that the product attributes and profiles are significantly different in biologically, toxicologically, and clinically meaningful ways. In this latter case, as already referred to in the European guidance cited above, a full registration data set including extensive toxicology, clinical studies and a Phase IV monitoring program would be expected to support the initial registration decision. The approach outlined above provides a conceptual framework for generating key data sets to support registration dossiers for a "follow-on" biologic; the extent and quality of the data will drive the registration conclusion. Furthermore, the comparative data would be generated in a context that allows responsible scientists and regulatory authorities to arrive at a conclusion that will assure patient safety and allow the introduction of new therapeutic options to the marketplace.

References:

1) Scientific Considerations Related to Developing Follow-on Protein Product: Public Workshop, September 14-15, 2004, Rockville, MD.

2) Proposed DIA/FDA scientific workshop on Follow-on Protein Products announced to be held during Q1/05; The Pink Sheet, August 9, 2004, p. 10.

3) CPMP/BWO/3201/00: Note for Guidance on Comparability of Medicinal Products Containing Biotechnology-Derived Proteins as Drug Substance, Effective March 2002.

4) Green, James D., Tsang, Lincoln, and Cavagnaro, Joy A., 'Generic' of 'follow-on' biologics: scientific considerations and safety issues, Expert Opin. Biol. Ther. 3, 1019-1022, 2003.

5) Schellekens, H., When biotech proteins go off-patent, TRENDS in Biotechnology, 22(8), 406-410, 2004.

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