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30 May, 2008

European Medicines Agency
Westferry Circus, Canary Wharf
London, E14 4HB, UK
BY EMAIL TO alexis.nolte@emea.europa.eu

RE: Concept Paper on a Guideline on the Chemical and Pharmaceutical Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials, Doc. Ref. EMEA/CHMP/BWP/466097/2007

Dear Sir/Madam,

The Biotechnology Industry Organization (BIO) appreciates the opportunity to provide comment on the European Medicines Agency's (EMEA's) *Concept Paper on a Guideline on the Chemical and Pharmaceutical Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials.* BIO represents more than 1,150 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products.

GENERAL COMMENTS:

During the preclinical development stage, studies are conducted that begin to form the basis for selection of a molecule with characteristics that are appropriate for clinical development and the conduct of requisite Investigational New Drug Applications (IND/CTX)-enabling studies. At the conclusion of these studies, data must be provided to demonstrate that the test material used in the IND/CTX-enabling studies is "representative" of that intended to be used for Phase I, while acknowledging that the processes for manufacturing and characterizing the material will continue to evolve during development. We suggest that, for this test material, the following general concepts be captured in the guideline:

- Recognizing that many biologics are heterogeneous and are in fact "mixtures", all species present in the Phase I material should ideally be present in the test material used for IND/CTX-enabling studies. The significance of "outlier" species should be evaluated on a "case by case" basis with due consideration to the projected therapeutic ratio.
- Structure/activity data generated during the preclinical stage should be considered. These data should include: biochemical characterization data, biological activity data that are related to presumed mechanism of action (MOA), pharmacokinetic data, and pilot safety results. The generation of these data should be directed by a prospective "Product Comparability Program" that is initiated at the IND/CTX stage and should follow the philosophical principles of "Quality by Design".
- The pharmacokinetic profile of the candidate molecule should meet the intended "frequency of dosing" requirements envisioned for support of the clinical "proof of concept" study(ies).
- Ideally, the cell line intended for Phase I production should be used.
- The formulation intended for use in Phase I should be closely approximated. For example, if a liquid formulation is intended to be used in Phase I, a liquid or reconstituted lyophile formulation containing the same excipients and formulation strengths should be approximated in the IND/CTX-enabling studies. The significance of minor formulation changes should be evaluated in the context of the available scientific data.
- For parenteral formulations, standard aseptic techniques should be employed to assure sterility of the final formulation. Quality standards should be met for an acceptable level of endotoxin and bioburden.
- The test material used for IND/CTX-enabling studies can be produced under "non-GMP" conditions; however, standardization of critical conditions reflecting "good scientific practices" across programs is required. Appropriate documentation should be available to satisfy associated compliance requirements.

SPECIFIC COMMENTS ON CRITICAL ASPECTS OF QUALITY:

1. The extent of information needed about the structure of a molecule and the quality characteristics of the drug substance.

It is very important to have a clear and balanced view of the information required at the beginning of a Phase I clinical investigation, including a product's key product characteristics, because this will facilitate and guide future process changes. The process by which a biologic is made can undergo many changes during the pre-IND/-CTX, IND/CTX, Phase I, II and III stages. In some cases, these process changes often extend well into the post-marketing setting. During the course of these stages, it is not unusual for changes to occur to the cell line, formulation, and various components of the production or purification scheme (the driving force behind the need to change a specific process fermentation or purification scheme is often the desire to improve product quality characteristics and/or cost of goods structure). To facilitate and guide these changes, sponsors should be encouraged to define a product's key product characteristics and

methods for assessment early in development. Key product characteristics govern potency, safety, and efficacy, and thus, influence therapeutic ratio and risk estimates made for the biologic.

Note that while product comparability evaluations typically employ a tiered approach, they can include biochemical, bioactivity, and pharmacokinetic studies. If major differences in comparability profiles are discovered between the pre-IND/-CTX and clinical test materials, it may be necessary to repeat the pivotal preclinical safety studies to ensure safe use conditions are supported.

2. **Information needed on cell banks.** Typically, a full characterization of the Master Cell Bank (MCB) is available for submission at the time of the IND/CTX filing. The Working Cell Bank (WCB) may be ready for use, as well, but in most cases isn't engaged until a need for test material "resupply" or to fund later-stage clinical trials.

3. **The extent of characterization needed for process and product related impurities.** The development of "standard" or direct specifications for parent molecule, multimers, aggregates, fragments (e.g., light chain, heavy chain, etc), host cell proteins, DNA, viral particles, and leachables should be encouraged for product classes and justified by the Sponsor. Indirect specifications may reasonably be developed for certain product-related substances (e.g., acidic/basic variants). Sponsors should have an appropriate level of understanding of how these substances may impact product potency and/or safety.

4. **The extent of information needed on the manufacturing process, the control of critical steps and in-process controls.** The utilization of a "platform approach" can provide valuable information on what to expect from critical steps and what in-process controls are adequate to meet the set specifications. Sponsors should be able to specify what product quality can be achieved with the "unit operations" available.

5. **The extent of development and/or validation of the manufacturing process that is required prior to and during clinical development.** The guideline should encourage the use of "platform approaches" whenever possible to minimize the amount of process development required and to reduce the associated process and product risk. This would enable reduction of timelines and the amount of new development effort required within a particular product class**.**

6. **The extent of qualification/validation required for the analytical procedures.** All analytical methods should be satisfactorily robust to be considered qualified at the time of IND/CTX submission. All assays will be validated at the time of Process Validation Reports (PVRs).

7. **Setting and justification of preliminary specifications.** Sponsors should provide an appropriate justification for early specifications as part of the

IND/CTX. At BLA/MAA submission, preliminary final specifications should be provided, with a commitment to refine these specifications once further experience is acquired after a mutually agreed-upon number of commercial runs.

8. **The requirements for stability data.** In general, a minimum of 30 days stability data on drug product is recommended for IND/CTX filing. Longer-term data from ongoing stability studies should be provided for later stage products. For initial BLA/MAA filing, a minimum of 6 months stability data is recommended; supplementation of the application with 12-month data during dossier review should be acceptable. It is suggested that all ICH temperatures (i.e., refrigerated/frozen, room temperature, and an accelerated temperature) should be studied.

9. **Changes that require a substantial amendment to a clinical trial application.** Significant process changes should be avoided during the conduct of pivotal registration trials, particularly during Phase III. If changes are made, extensive product comparability assessments are required. Depending upon the data, it is possible that pivotal studies would have to be repeated if the test material used in Phase III is concluded to be significantly different from commercial material. Examples of situations when additional nonclinical and/or clinical evaluation may be required include: changes in cell line, production phase bioreactor or site, or production scale, and characterization results that indicate impact to critical product quality attributes.

CONCLUSION:

BIO appreciates this opportunity to comment on EMEA's *Concept Paper on a Guideline on the Chemical and Pharmaceutical Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials.* We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Sara Radcliffe
Vice President, Science and Regulatory Affairs
Biotechnology Industry Organization