26 August 2013

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Submission of comments on: **Docket No. FDA-2013-D-0575 Guidance for Industry Expedited Programs for Serious Conditions—Drugs and Biologics**

Dear Sir or Madam,

Thank you for the opportunity to comment on the proposed Guidance for Industry Expedited Programs for Serious Conditions—Drugs and Biologics.

ISPE is pleased to make both general and specific comments to the guideline as detailed in the following pages. There were several issues raised by ISPE members in relation to manufacturing development issues that may lag the clinical development program. These issues were discussed in detail among our ISPE members and we submit comments on those issues we found most significant.

The International Society for Pharmaceutical Engineering (ISPE) is an individual membership Society of more than 20,000 professionals involved in the manufacture of pharmaceuticals and related products. All scientific and technical areas of the pharmaceutical manufacturing industry are represented among the ISPE Membership. ISPE is committed to creating a forum for uniting the world's pharmaceutical manufacturing community and regulators.

Thank you again for the opportunity to comment on the proposed draft guidance. Please feel free to contact me if you have any questions

Yours sincerely,

Nancy S. Berg
President/CEO, ISPE

Proposed Regulation/Guidance Document:

Guidance for Industry Expedited Programs for Serious Conditions––Drugs and Biologics, Docket No. FDA-2013-D-0575

Comments submitted by: ISPE – International Society for Pharmaceutical Engineering

General Comments:

1. Section IX: General Considerations—A. Manufacturing and Product Quality Considerations

   Comment: FDA states that the sponsor of a product that receives an expedited drug development designation will probably need to pursue a more rapid manufacturing development program to accommodate the accelerated pace of the clinical program, and lists activities a sponsors should take to ensure availability of quality product at the time of approval. It also states that sponsors allow for earlier submission of the CMC section for timely review and inspection planning.

   Although FDA offers the opportunity for "frequent communication during development" to meet "manufacturing development and product quality goals", the draft guidance offers no indication of flexibility or willingness to work with the sponsor on manufacturing development issues that may lag the clinical development program. In addition, proposing an earlier submission of the CMC section for a breakthrough product ignores the compressed manufacturing development time frames needed for the accelerated pace of clinical development.

   Proposed Change: In addition to more frequent communication with sponsors on manufacturing issues, FDA should clarify those aspects of manufacturing development that could be negotiated with the sponsor for completion either during review of the marketing application or as part of a post-approval commitment.

   This could include for example, the use of a Post-approval Lifecycle Management Plan (PALM) that could be part of the marketing application and provide detailed timelines, deliverables, and types of regulatory filings for completing activities, such as:

   - Scale-up phase 3 clinical lots to commercial scale for launch with bridging comparability study. The possibility to launch from clinical site at a reduced scale with clinical QC release, and transfer to commercial site and commercial QC post-approval
   - The possibility to launch with provisional control system that ensures consistent product, and upgrade the control system post-approval after more manufacturing experience and completion of process validation, i.e., filing with more tests initially, and justifying elimination of some post-approval; filing with broader IPC and product specification acceptance criteria; and tightening post-approval for specifications that demonstrate process consistency

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- Launch commercial process with limited experience and optimize post-approval with comparability protocol
- Launch with phase 1-2 formulation and optimize post-approval with comparability protocol. Launch with reduced real time stability for commercial material and leverage stability from development lots and predictive modeling of small molecule degradation profiles
- Leverage life-cycle validation principles "continued verification" to release batches concurrent with manufacture of initial conformance batches

The guidance should also address willingness of the FDA to work with a sponsor to ensure flexibility of their Pharmaceutical Quality System to accommodate the accelerated manufacturing development activities for a breakthrough product.

The guidance should offer a pathway for coordinating the timing of inspections related to these activities and for setting the expectation how to approach documents that are incomplete pending the completion of various activities that may have been pre-negotiated through the project manager.

Specific Comments

Section	Line Number	Comment/Recommendation
VII B - Accelerated Approval Endpoints	508	This section does a good job of discussing the relationship between a mechanistic understanding of the drug mechanism of action on the disease state and the differentiation between true clinical endpoints and surrogate endpoint however there is no discussion of how to handle analytical testing uncertainty associated with limited understanding of mechanism of action. **Recommendation** Include a discussion of potential surrogate analytical tools, such as bioassays for biologics, which along with quantitative analytical tools such as LC/MS can be used to characterize and control the in-vitro testing against a poorly defined clinical endpoint.
VII C - Evidentiary Criteria for Expedited Approval	584	This section discusses potential surrogate clinical endpoints as a basis for approval by saying "Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval." In **section A- Line 617** the section goes on to discuss the need to understand the disease process and the relationship between the drugs effect and the disease process (line 650). However they do not offer a pathway for establishing this level of understanding. **Recommendation** The agency should define what level of studies it will want to see, at a minimum, to support mechanistic understanding on the disease state. As an example, for early promising drugs where the mechanism of action is not

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		known ADME studies could be performed to determine if there is a shift in metabolite concentration between the animal and human models. A radiolabeled ADME study in humans, using a single dose of radioactive parent drug has been the mainstay study enabling comprehensive identification and quantification of drug metabolites. Before the human ADME study can be conducted, a whole body autoradiography study in rats is required to obtain dosimetry data. Since ideally the dose selected for the human study should be clinically relevant, typically these radiolabel ADME studies are conducted after enough efficacy data is available to estimate a clinically relevant dose. In this case there will be limited clinical efficacy data to evaluate, escalating the need for ADME studies early. Failing to identify unique or disproportionate human metabolites early will be critical to determining if additional toxicology studies will be required. The guidance should include additional specific recommendations that can be applied as part of a Risk management analysis to evaluate the potential clinical risk.
	614-15	**Line 614-615** states: "However, this guidance 614 does not address clinical evidence requirements because they are not readily generalizable." **Recommendation** Potential organizations which may be identifying prospective molecule candidates can run the spectrum from university spin-off to large pharma-biopharma. The guidance should specify at a minimum what data would be required at the time of evaluation for accelerated approval candidacy. For example what, if any animal pharmacology and toxicology studies would be required as part of the review process? What material characterization studies should be complete? Some definition of potentially supportive data would assist candidates in determining if the minimum requirements for evaluation are in place.
Section IX: General Considerations—A. Manufacturing and Product Quality Considerations		**Line 584** states: "Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval." This section does not make any reference to the compliance expectations for drugs under this program. There should be some discussion of the state of maturity of candidate organizations' quality management systems. Realistically this is the most difficult element for small or emerging organizations to implement. Post marketing studies will not have the same impact if they are not complemented by a strong quality system. **Recommendation** State that the organization will have implemented quality systems consistent with supporting Phase 2 clinical program at the time of BLA/NDA submission. This would infer basic systems had been created and implemented. In addition, it would also allow technical development to continue in terms of method development and a control strategy. It should further state that upon approval the manufacturer must implement commercial manufacturing studies as it moves through post approval marketing studies as agreed to as part of the

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Section	Line Number	Comment/Recommendation
		BLA/NDA submission.

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