



Schering-Plough

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June 30, 2004

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

Re: Docket No. 2003D-0571; Draft Guidance for Industry on Drug Substance:  
Chemistry, Manufacturing, and Controls Information

Dear Sir/Madam:

Schering-Plough has reviewed the Draft Guidance for Industry on Drug Substance: Chemistry, Manufacturing, and Controls Information and we welcome the Agency's initiative in issuing this draft guidance, which is intended to replace the current 1987 guidance. We believe that revision of the 1987 guidance offers the opportunity for Industry and the FDA to align on critical areas of importance to both Industry and the FDA, and recognize the scientific and technical advances that have been made since the original guidance was published. In this communication we are providing comments on the draft guidance. We also support PhRMAs comments and the suggestion that more discussion between industry and the FDA is needed on conceptual issues.

1. A large amount of detail is being requested in the Process Flow Diagram (Lines 406-436) which may make the diagram confusing. We propose that the focus should be on a schematic outline of chemical transformations, not the detail of the individual steps. Much of what is requested is included in other sections of the document and could be deleted; i.e., reference to process controls, reference to operating parameters and expected yield.
2. Scale of production (line 441) should not be a requirement. Requiring this information would make it a regulatory requirement to update the filing for every scale change made.
3. The type of equipment used should only be required when it is outside of the normal types of processing equipment used in API manufacturing. We believe that this information would add no value to the submission but could substantially increase the burden on industry to maintain the accuracy of submissions.
4. The reference to the combination of batches (line 471) should be restricted to cases where the combination of materials occurs prior to analysis or release. Most

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API processes involve the combination of batches of one intermediate to the next step, since batch sizes are usually not "one for one." This combination of batches generally occurs post-analysis or release.

5. We propose a revision of lines 488-490 to read "A risk analysis should be provided if bovine derived materials from bovine spongiform encephalopathy (BSE) countries... are used or manipulated in the same facility."
6. Designation of critical steps in the flow diagram is repetitive and unnecessary in view of the need to incorporate this in the process description and Section S.2.4 (line 540).
7. Lines 810-812 "Tests performed in-process in lieu of testing the drug substance..." should be deleted. This would be a cumbersome specification for which it could be very difficult to compile the data.
8. In section IV.D., lines 814-864, are divided into three categories, "Intermediates," "Postsynthesis Materials," and "Unfinished Drug Substance." It is unclear what the intent is for these three categories since the technical requirements do not differ for these three groups. We think these terms should be abandoned since the differentiation does not appear to add any value.
9. Please clarify if the data requested in lines 1111-1114 (and footnote 18) are not required when the supplier is internal to the drug manufacturing company.
10. In Table 1, remove the requirement to include the brand for the particle size analyzers. Equipment brands are not included in the filing.

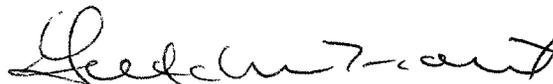
Overall, we have a number of substantial concerns on Attachment 1 on Starting materials, and recommend that the FDA open a dialogue with Industry on this topic with a view to rewriting the section in its entirety to be more consistent with a science based approach. In the event the Agency does not pursue this path, we are providing comments below on specific aspects of this Attachment

11. Please clarify why an existing drug substance cannot be used as a starting material (lines 1683-1685). We believe that drug substances are well understood, well-controlled and are most consistent in terms of process and quality such that they would be reasonable choices as starting materials.
12. We agree that chemicals with a significant non-pharmaceutical market need to be included as starting materials (lines 1696-1719), since finding suppliers who make this under GMP may not be practical. However, we see no differentiation between these chemicals and the "non-pharmaceutical market" chemicals in terms of their suitability as starting materials. What should be paramount in this selection process is an understanding of the quality for these starting materials and the appropriateness of the controls around them, irrespective of source.

13. We propose that section 1.A. of Attachment 1 focus on control of the process and the understanding of starting material and intermediate quality, in particular the number of analytical evaluations applied to different chemicals during downstream processing, rather than propinquity.
14. Line 1805, "Moreover, a chemical with a complex molecular structure...can also increase the risk." with regard to starting materials is too broad a generalisation. Some complex structures, for example steroids, are often used for starting materials. We do not believe that structural complexity per se should be a criterion for starting material selection
15. We disagree that Chiral HPLC (line 1816) is an advanced technique, and propose that this be deleted from the list of techniques for which use of would indicate that a chemical is not an appropriate candidate for a starting material.
16. The specifications outlined in lines 1859-1863 are quite stringent. Since it is already a requirement to identify and qualify impurities in drug substances, this level of specification is not necessary. If it is required, who would be responsible for specifying these impurities as this would be more stringent than existing specifications?

Schering-Plough appreciates the opportunity to comment on this guidance document and hope that we hope that you will take our comments under consideration when finalizing the document.

Sincerely,



Gretchen Trout  
Director, Regulatory Liaison and Policy  
Global Regulatory Affairs