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

Att'n: Jeffrey Shuren, Assistant Commissioner for Policy

**RE: Federal Register Docket Number 2005D-0286**  
***Chiron Corporation Comments on the Draft Guidance for Industry on  
Investigational New Drugs; Approaches to Complying with Current Good  
Manufacturing Practice During Phase 1***

Dear Mr. Shuren:

Chiron Corporation hereby submits comments on the *Draft Guidance for Industry on Investigational New Drugs; Approaches to Complying with Current Good Manufacturing Practice During Phase 1*.

Our first comments pertain to the general philosophy espoused in the draft guidance. These general comments are followed by comments and suggestions on specific points in the text, given in the same order as the text to which they refer.

Should you have any questions regarding the information submitted herein, please contact me at (510) 923-5740 or, if I am unavailable, Jeri Beltman, Ph.D. at (510) 923-5225 [fax (510) 923-3344].

Sincerely,

CHIRON CORPORATION



Gia D. DePillis, Ph.D.  
Associate Director, Regulatory Affairs

Enclosures: Original + 1 copy

2005D-0286

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## 1. General Comments

- Our understanding of FDA's intention behind the proposed rule and supporting draft guidance is to facilitate early pharmaceutical development of investigational drug products by exempting manufacturers from following 21 CFR Part 211 while still adhering to principles of CGMP as codified in 501(a)(2)(B) of the FD&C Act. This seems to us to be consistent with FDA's initiative, *Pharmaceutical cGMPs for the 21<sup>st</sup> Century: a Risk-based Approach*, but:
  - this message is lost in Paragraph 3 of Section II. *Background*. It seems to us that the "21<sup>st</sup> Century Initiative" is at the crux of the new proposed rule. We feel that this connection should be better emphasized, just as the philosophy of an "incremental approach" to manufacturing controls during development should be greatly emphasized, perhaps even more than it is in Paragraph 2 of the same section.
  - this philosophy is divergent from the recent EMEA (Clinical Trial Directive) requirement that clinical trial materials be manufactured essentially as stringently as commercial products. Although we realize that there is no obligation for FDA to harmonize all regulations and practices with the EU or other worldwide regulatory authorities, we think it would be helpful to discuss in the draft guidance the phase I exemption from Part 211 in the context of FDA's risk-based initiative and how it interfaces with ICH and EU policies.
- Although we appreciate that a guidance document must apply to all situations and therefore must be general and flexible, a guidance document becomes more useful if this tendency is balanced with a bit of practical information, perhaps in the form of specific examples pertaining to common situations. We felt that section VI.D. *Sterile Products/Aseptically Processed Products* was the most helpful in the draft guidance in this respect, with detailed recommendations that befit the seriousness of sterility as an attribute of for example injectable products. Perhaps other sections, most notably V.C. *Facility and Equipment*, could provide a bit more detail or at least some examples of "appropriate" facilities and equipment.
- Please define key terminology in the Glossary and be more specific and consistent throughout the document in the use of that terminology. For example, we suggest that definitions for "biological" and "biotechnological" products be included in the Glossary, as well as for "drug substance" as it applies to biologics.
- Mention of and expectations for process and analytical validation are not addressed in this draft guidance. We believe that the guidance should cover this topic, pointing out that expectations for process and analytical validation are lower in phase I clinical development than for later-stage or commercial manufacturing process development per the "incremental" philosophy.

## 2. Title of the Draft Guidance Document

- We believe it would be more accurate to replace "during" with "for" in the title of the draft guidance, e.g. *INDs—Approaches to Complying with CGMP For Phase 1*. The word "during" is misleading in the context of common practices for manufacturing campaigns, as most manufacturers initiate their campaign to manufacture phase I clinical materials well before phase I clinical studies are initiated.

### 3. Section III Scope

- Third paragraph, first sentence (“*The guidance applies to investigational products whether they are produced in small- or large-scale environments because such studies are typically designed to assess tolerability or feasibility for further development of a specific drug or biological product*”):
  - We wondered why the word “environments” was chosen instead of “facilities”, which is usually the first word that comes to mind when describing the physical place where pharmaceutical R&D and manufacturing takes place – even in small companies. FDA’s word choice sparked much discussion and debate among our team about whether or not the word was chosen deliberately to convey something about FDA’s philosophy that we did not (but should better) understand. Our curiosity was further piqued when, in the last paragraph of Section III, the more typical word “facility” is used to refer to the place where a “series of [manufacturing] steps...” would occur.
  - We surmised that “such studies” refers to phase 1 clinical studies, but there is no antecedent in the sentence regarding clinical studies. For increased clarity, we suggest that “phase 1 clinical studies” replace the phrase “such studies”.

### 4. Section IV Statutory and Regulatory Requirements

- In our reading of the regulations and our current understanding of FDA’s intention behind the new proposed rule and this draft guidance, the examples in Paragraph 3 for how “certain of the requirements of 21 CFR Parts 211...were directed at commercial manufacturing” are not the only examples of provisions in Part 211 that might not apply to the manufacture of phase 1 investigational materials. In our understanding, many provisions of Part 211 Subparts C and D (Buildings and Facilities and Equipment, respectively) also could be seen to be more specific to commercial manufacturing. If FDA agrees with this viewpoint, it would be helpful if more examples such as these were to be cited to better convey the intention of the proposed rule and how it fits into the existing legal and regulatory framework.

### 5. Section V Recommendations for Complying with the Statute

- We feel that the formatting in the introductory portion of this section (i.e. the paragraphs preceding subsection V.A.) renders it confusing and difficult to read, with important messages becoming obscured. The following are some suggestions to improve the readability of this portion:
  - Paragraphs 2, 3, and 4 (beginning with “During product development...”, “Adherence to QC procedures...”, and “Written procedures that...”, respectively) should be combined into one paragraph and the three bullets converted into a text list. Our rationale is that these paragraphs are part of a discussion of the same topic, the importance of QC procedures; further, the bullets distract.
  - Similarly, Paragraphs 5 and 6 (beginning with “Producers may have...” and “A number of technologies...”, respectively) should be combined into one paragraph. It would be acceptable to have the bulleted list in Paragraph 7 remain bulleted.

- Again, Paragraphs 8, 9, and 10 (beginning with “Because the sponsor...”, “We recommend...”, and “A formal evaluation”) should be combined into one paragraph. We suggest that Paragraphs 9 and 10 be combined by making the following change:

- *We recommend a formal evaluation of the production environment to identify potential hazards **and to take** appropriate actions prior to and during production to minimize risks and safeguard the quality of the investigational product*

#### **6. Section V.C. Facility and Equipment**

- We feel that the phrase in Bullet #1 “clean environment” is too vague, requiring more specificity for clarification. What exactly would be the burden of testing to determine that an environment is clean?
- Are there any testing requirements for facilities and equipment to be used in phase I investigational drug product manufacturing?

#### **7. Section VI.B. Multi-Product Facilities**

- Second sentence (“*However, the same area or room could be used for multiple purposes, including production of other investigational products...*”):
  - We suggest that this sentence be edited to indicate that production of other products does not happen at the same time as the desired investigational product: “*However, the same area or room could be used for multiple purposes, including **nonconcurrent** production of other investigational products...*”

#### **8. Section VI.C. Biological and Biotechnological Products**

- We believe that it would be less confusing if the first paragraph in VI.C.1., which calls out exceptional products, were to be placed at the end of section VI.C.1. Section VI.C.1. would then start with the current second paragraph, which enumerates important characteristics of biologics (that distinguish them from small molecule drugs) that warrant being addressed in a separate section in the draft guidance.