



ABBOTT

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

Ref: Docket No. 2005D-O286 - Draft Guidance for Industry on Investigational New Drugs; Approaches to Complying with Current Good Manufacturing Practice During Phase 1

To Whom it May Concern:

Abbott is very pleased to have the opportunity to provide comments on the Draft Guidance for Industry on Investigational New Drugs; Approaches to Complying with Current Good Manufacturing Practice During Phase 1 published on January 17, 2006 in the Federal Register. The comments submitted to the Draft Guidance are consistent with our comments submitted on the Proposed and Final Rule Docket No. 2005N-0285.

We thank the Food and Drug Administration for your consideration of our comments. Should you have any questions, please contact Kathy Wessberg (tel: 847-938-1264, e-mail: kathy.wessberg@abbott.com).

Sincerely,

Zena Kaufman
Encl: Comments

2005D-0286

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ABBOTT COMMENTS TO FDA ON

Docket No. 2005D-0286

COMMENTS

General Comments:

Overall, Abbott considers this to be a helpful Guidance. This establishes requirements for Phase 1, but in practice it can be difficult to differentiate between the clinical phases with respect to use of investigational materials. The same material, particularly the Active Pharmaceutical Ingredient (API) may be used in Phase 2 if the outcome of Phase 1 is positive. Consequently Abbott encourages the FDA to develop further Guidance for Phases 2 and 3, and to reduce the impact of 21CFR211 on these later Phases of drug development. Additionally Abbott encourages harmonization with the European GMP Guidance for Investigational Medicinal products (Annex 13 to Volume 4, Good manufacturing practices).

Abbott believes that throughout drug development, the basic principles of GMP must apply, namely:

- Avoidance of cross contamination with other products
- Prevention of microbial contamination
- Assuring authenticity and appropriate purity of investigational materials

As knowledge evolves during the development process, so will the specific GMP requirements in terms of system control and documentation. Thus the Quality System used to prepare Investigational Materials must be capable of effectively and efficiently managing the expected change, through the incremental approach previously suggested by the Agency, in contrast to commercial operations where change must be tightly controlled or even avoided.

In several parts of the Guidance, reference is made to "certain exploratory products" or "most investigational drugs" being exempted from the 21CFR211 requirements. It would be helpful to have some clarification of the Agency's thinking of what the implied exceptions would be.

The Quality Control (QC) function is described in a number of places. Abbott believes it is important to differentiate between QC and the wider concept of Quality Assurance (QA), and to introduce the QA concept for investigational materials.

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Specific Comments:

Page	Section	Line	Recommendation
1	I. Introduction	31	"Most investigational drugs" is not defined. If the agency has specific exceptions, these need to be specified, or the word "most" should be deleted.
2	II. Background	75	"Certain exploratory products" is not defined. If the Agency has specific exceptions in mind, these should be specified, or the word "certain" should be deleted.
3		81	<p>At present, all portions of 210 and 211 could be considered applicable, so this lends credence to our desire for the Agency to issue Guidance for these later Phases. It would be helpful to re-emphasize that the Agency is open to an incremental application of 210 and 211 until the relevant Guidances are established.</p> <p>Recommend changing to: "Phase 2 and 3 production will be subject to an incremental application of those portions of 210 and 211 that are applicable."</p>
4	IV. Statutory and Regulatory Requirements	136	"Most drugs" is not defined. If the Agency has specific exceptions in mind, these should be specified, or the word "most" should be deleted.
4/5	V. Recommendatio ns for complying with the Statute	158	"Most phase 1 studies" is not defined. If the Agency has specific exceptions in mind, these should be specified, or the word "most" should be deleted.
5	V. Recommendatio ns for complying with the Statute	162- 171	<p>Abbott believes that quality control needs to be expanded to the Quality System concept that is included in ICH Q7A. For example, adherence to QC procedures does not occur through having equipment that is adequately controlled. We suggest that the guidance be amended to present the characteristics of an effective Quality System that is appropriate for investigational products. Aspects of the system that might be included are:</p> <ul style="list-style-type: none"> • Written procedures • Risk management • Appropriate control of equipment • Recording of data • Maintaining the integrity of clinical trial supplies



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Page	Section	Line	Recommendation
6/7	V.B. Quality Control Function	224- 251	Currently makes no differentiation between QC (Sampling, Testing, and Inspection) and QA (overall assurance of Quality). The QA function should be responsible for releasing or rejecting each clinical batch. In addition, we are uncomfortable with the concept of the same individual being responsible for both production and QC. Specific recommendations for change follow:
6	V.B. Quality Control Function	226 and 227	The term "QC plan" suggests a specific plan for each lot of product. We believe that it is important for each producer to establish a Quality System that defines the routine responsibilities and systems used to prepare investigational materials. Also need to bring forward the important statement in Line 251 Recommend rewrite: "It is important to note that Quality is the responsibility of all personnel involved in the manufacturing, packaging, and testing of investigational products. We recommend that every producer establish a written Quality System. For example, a sound Quality System should provide for the following functions: "
6	V.B. Quality Control Function	229- 231	Recommend rewrite: <ul style="list-style-type: none"> • "Establishing acceptance criteria, that are appropriate with regards to patient safety and extent of knowledge about the product, for the various components used in production of a product (Active Pharmaceutical Ingredients, excipients, primary packaging materials, intermediate dosage forms) and for the bulk and packaged product. • Responsibility for sampling, inspection, and testing of starting materials, intermediates, and product (Quality Control)"
6	V.B. Quality Control Function	232 - 233	OK as written
6	V.B. Quality Control Function	234 - 236	Add: "This is generally considered to be a Quality Assurance activity."



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Page	Section	Line	Recommendation
6	V.B. Quality Control Function	237 – 238	<p>Corrective action may not always be necessary, and will vary in extent.</p> <p>Recommend rewrite:</p> <ul style="list-style-type: none">• “Responsibility for appropriate investigation and corrective action if unexpected results or errors occur during production, or in response to complaints.”
6	V.B. Quality Control Function	239 – 243	<p>This section seems to be combining considerations of both functional separation, and separation of activities. In order to avoid contamination of product with such things as laboratory reagents, we believe it is necessary to be more specific.</p> <p>Recommend rewrite:</p> <p>“We recommend that testing activities are performed separately from production activities in order to avoid mutual contamination.” <i>(This addresses the location issue, consider organization in next paragraph)</i></p>
7	V.B. Quality Control Function	245 – 251	<p>This section should address the organizational considerations. The last sentence of the current section (Line 251) is too important to place here, and should be expanded to include testing. It could be helpful, and might address the Agency’s concern with respect to smaller organizations, to assign an individual as responsible for product release, similar to the concept of the ‘Qualified Person’ in the EU.</p> <p>Recommend rewrite:</p> <p>“We recommend that QC responsibilities be performed independently from production responsibilities. The designated individual(s) responsible for product release should independently attest that the product has been manufactured in compliance with this Guidance and the filed IND.”</p>
9	V.I. Recordkeeping	374	<p>The phrase “All quality control functions” is vague, and needs clarification. It is also redundant to lines 369-370. We recommend deletion of this phrase.</p>



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Page	Section	Line	Recommendation
11	VI.B Multi-Product Facilities	427- 429	<p>“We recommend that the implemented controls be <u>assessed</u> periodically to evaluate their effectiveness” is not clear as an “assessment” can imply many activities. We recommend “assessment” be replaced with the word “reviewed” for clarity.</p> <p>Proposed new wording: “We recommend that the implemented controls be <u>reviewed</u> periodically to evaluate their effectiveness”</p>
13	VI.D. Sterile Products/ Aseptically Processed Products		<p>It is not specified in the Guidance, but for products that are <u>not</u> terminally sterilized by Heating in an Autoclave 121°C/15min, Abbott believes the sterilization process needs to be qualified. For an aseptically filled product, even in Phase 1, the filling procedure, although it may be manual, needs to be qualified by media runs.</p>
13	VI.D. Sterile Products/ Aseptically Processed Products	518- 519	<p>The monitoring of environmental conditions is not mentioned, but would be important in order to conduct the investigations of sterility test failure in lines 551-553.</p> <p>Recommend amendment: “Disinfecting the entire aseptic workstations and monitoring of environmental conditions as appropriate. . . .”</p>
15	Glossary	572- 573	<p>Definition of “Component” does not match the description given in the body of the document, Lines 229-231. Needs to include packaging commodities.</p>