



March 20 2006

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

Docket No. 2005D-0286

Re: Draft Guidance for Industry on Investigational New Drugs; Approaches to
Complying with Current Good manufacturing Practice During Phase 1. January 2006

Dear Sir or Madam,

The above referenced FDA draft Guidance has been reviewed by scientists at Johnson & Johnson Pharmaceutical Research, LLC. The following general comments are provided for your consideration. Further, a table of specific comments on a line-by-line basis is attached.

General Comments

- We support the development of this guideline and believe there is a consensus that there should be incremental application of CGMP expectations throughout clinical development.
- Without proper guidance from FDA on this topic, we believe that there is no differentiation between Phase 1, Phase 2, Phase 3 CGMP and commercial CGMP expectations.
- Patient safety is the central focus for the Industry regardless of the phase of clinical development. Throughout development, the basic principles of CGMP must apply: assurance of authenticity and appropriate purity of investigational materials, prevention of microbial contamination, and avoidance of cross contamination with other materials.
- There should be consistent definition and application of specific concepts and terms used throughout the guidance.
- There should be a clear specification of what is not required for Phase 1 CGMPs.
- Where possible there should be avoidance of vague terms like ‘most drugs’ or ‘most phase 1 studies’. Use of examples of exceptions would benefit the application of this guidance.

- There should be alignment of CGMP expectations in this draft with other FDA draft guidances as they are issued.
- This draft should be harmonized with existing international guidances like ICH Q7A and Q9, EC Annex 13, and EMEA CHMP/QWP/185401/004

The attached table lists specific comments on a line-by-line basis.

We greatly appreciate the opportunity to comment on this draft guidance and look forward to working closely with the FDA on this and future documents. If you have any questions or need assistance, please contact me directly at 609-730-7609

Sincerely,

A handwritten signature in black ink that reads "Thomas W. Schultz, Ph.D." The signature is written in a cursive style with a large initial 'T'.

For Christopher C. Kowtna, M.B.A., M.S.
Associate Director,
Global Regulatory Affairs
Chem. Pharm.

**Johnson and Johnson Pharmaceutical R&D comments on FDA's
Guidance for Industry
INDs-Approaches To Complying with CGMP During Phase 1
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	Section	Line	Recommandation
2	II Background	66	No explicit advice/suggestion to make use of risk and science based (e.g. ICH Q7A, ICH Q8 and ICH Q9) approaches for complying with cGMP noted. There is only a reference to the Agency's cGMP for the 21st century initiative in the background section, but no suggestions in the specific guidance sections. Perhaps cross-referencing the Exploratory IND process to appropriate ICH guidelines should be considered.
2	II. Background	75	What is meant by "certain exploratory products"? If the Agency has specific exceptions in mind, these should be specified, or the word "certain" should be deleted.
3	II. Background	80 – 81 53-68	"Phase 2 and 3 production will continue to be subject to those portions of 210 and 211 that are applicable." Additional clarity is needed on the intention of this sentence. Without additional clarification, it could be interpreted that phase 2 and 3 CGMP expectations are not dramatically different from commercial CGMP expectations (which does not align with the incremental CGMP approach mentioned earlier in this section-lines 53-68). We request that the Agency is more specific on the sections of 210 and 211 which are applicable and those, which are not.
3	II Background & III. Scope	80, 81, 91-95	Text of guidance in cited lines appears to be contradicting other sections in relation to production of Phase 2 and Phase 3 supplies. In these lines, the production supporting these phases is equivalent to commercial environment. This is not consistent with incremental approach in lines 57-68. Please clarify.
3	III. Scope	110	The list of references should also include the 'Guidance for Industry, Investigators, and Reviewers: Expletory IND Studies' Issued January 2006.
3	III. Scope	115	For the manufacture of API's, Q7A is mentioned as guidance on CGMP compliance, but in that document no consideration of risk is mentioned.
4-5	V. Recommendations for complying with the Statute	158-159 See also 75, 80, & 86	What is meant by "most phase 1 studies"? If there are specific exceptions in mind, these should be stated, or the word "most" should be deleted. Along these same lines, additional clarification is needed "for a variety of investigational new drugs manufactured in various situations."

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5	V. Recommendations for complying with the Statute	170	This guidance does not make clear whether the Agency expects equipment IOQ to be completed prior to manufacture of Phase I supplies. It implies that controls "might" be limited to adequate maintenance, calibration, documentation, cleanability, etc. Clarification would be valuable.
5	V. Recommendations for complying with the Statute	170 185	Equipment control is indicated in this line vs. qualification of equipment. This is not consistent with line 185, which indicates qualification. Guidance does not address analytical instruments and associated requirements. USP requires qualifications for instruments.
5	V. Recommendations for complying with the Statute	186- 188	This may not be consistent with EMEA expectations (e.g. "closed" process may not be completely closed when extraction final form-EMEA may likely still require appropriate buffer zone)-suggest rewording or deleting. General comment is that some principles in this document do not appear to align well with EU GMPs so Agency may need to clarify where EU or how GMPs may supersede this guidance.
6	V. Recommendations for Complying with the Statute	205	This bullet point should be revised to read: "The production environment should minimize potential hazards that could impact product quality and safety". Clarification is otherwise needed on "formal evaluation of the production environment to identify potential hazards". It is not clear if this is an expected documentation to support Phase 1 production environment in light of the controls covered in this guidance.
6	V. Recommendations for complying with the Statute	208- 380	It is suggested that a "side-by-side comparison table would be useful to easily illustrate the incremental nature of CGMP controls when compared with the existing statutes and regulations (21 CFR 210 & 211)
6	V. Recommendations for Complying with the Statute	212- 214	Clarification to help users determine the type and degree of risk assessment that is relevant/acceptable would be valuable. Known approaches like FMECA, HAACP, etc., should be mentioned as examples so that users are able to gauge the quality and formality of the deliverable
6	V.A. Personnel	216- 222	The current draft guidance is silent on the following topics: health habits, notification of illness, and wearing of protective apparel. These are relevant to manufacture of clinical materials for Phase 1 studies, hence, should be addressed in this section.

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6	V. B. Quality Control Function	239- 243	Clarify that established SOPs that accomplish these elements are acceptable in lieu of a plan.
6	V. B. Quality Control Function	237	We feel a need to better specify "unexpected results" and to restrict corrective action measures to results or errors that are categorized as critical during investigation. We propose the following wording; "responsibility for investigation of unexpected analytical results or errors occurring during production, and initiation corrective action if appropriate.
7	V. B. Quality Control Function	245- 251	The word "organization " in the paragraph "However, in limited circumstances, depending on the size and structure of an organization, all QC functions could be performed by the same individual. For example, in some small operations, it may be justified to have the same individual perform both production and QC functions, including release or rejection of each batch..." should be further qualified. For instance, a large corporation may have a unit of operation where this provision would be applicable/justified. Further, the criteria for waiving the requirement for an independent qc function should be based on a scientific (level of experience/education, etc. of personnel) and/or risk benefit rationale rather than a mere size/structure of an organization argument.
7	V. B. Quality Control Function	248- 250	The independent person should be designated as QC for the operation for the purposes of release of clinical supplies.
7	V. C. Facility and Equipment	253- 271	The current draft is silent on the topic of equipment qualification. The Agency should be explicit with respect to this topic considering that 21 CFR 211 does not mention equipment qualification requirements, yet qualification of equipment is expected for products on the market and investigational product in later stages of development.
7	V. C. Facility and Equipment	263	Further clarification regarding information on equipment / facility cleaning vs. expectation in a commercial environment would be very helpful.
7	V. D. Control of Components	273	The description of component in various parts of this guidance and relative to the requirements of section D does not align with the definition of component in the glossary (e.g. line 229 and line 572). We recommend line 229 be revised to read: "Responsibility for examining the various components and drug product containers and closures..." Line 273 should read:

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			“D. Control of Components and Drug Product Containers and Closures”
7	V. D. Control of Components	275- 278 279- 282	<p>In line with the comment above lines 275-278 should be revised to read:</p> <p>“We recommend there be written procedures describing the handling, review, and acceptance and control of components and drug product containers and closures used in the production of an investigational product. Components and drug product containers and closures should ...”</p> <p>Recording of components and drug product containers and closures may precede the assignment of an investigational product batch number or be used in more than one investigational product. The batch number would be cross-referenced at a later date. We suggest that the wording be changed to:</p> <p>“Records concerning an investigational product must contain or cross-reference relevant information on all components and drug product containers and closures used during its manufacture and packaging. Information about components and drug product containers and closures would include receipt date, quantity of the shipment, supplier’s name, component lot number, storage conditions and corresponding expiration or retest date. It must be possible to connect the component and drug product containers and closures information to a specific investigational product batch number.”</p> <p>The word “component” should be replaced with “ component and drug product containers and closures” throughout this section V. D. where appropriate.</p>
8	V. D. Control of Components	294- 296	If taken literally, this implies that “all” possible attributes may need to be tested, either by vendor or internally. It is suggested that that end of sentence include “...unless that attribute is deemed and documented as scientifically irrelevant to the Phase I nature of the formulation and/or investigation.”
8	V. E. Production and Documentation	300- 317	We suggest that ‘production record” should be qualified to include notebook (to bring alignment with 19.5 of ICH Q7A which states “...the production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other suitable means...”

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8	V. E. Production and Documentation	305- 309	This section addresses production, not laboratory testing. This sentence should be revised to read: "A record of production data that details the components and drug product containers and closures, equipment and procedures used including results of any in-process testing performed."
8	V. E. Production and Documentation	310	The guidance currently states: 'A record of changes in procedures and processes used for subsequent batches along with the rationale for any changes.' Changes are inherent to development. We propose to differentiate between non-critical and critical changes. 'Any' change is too broad. It is therefore suggested that that wording: 'A record of changes in procedures and processes used for subsequent batches along with the rationale for <u>critical</u> changes' is considered.
8	V. F. Laboratory Controls	323	For a Phase 1 IND using the existing "Guidance for Industry: Content and Format of INDs for Phase 1 Studies of Drugs, Including Well Characterized, therapeutic Biotechnology-Derived Products" analytical method validation data for specificity, sensitivity, and accuracy is not expected for submission. Suggest that a cross-reference to this existing guidance be used to describe the contents for Phase 1 IND submissions.
	V. F. Laboratory Controls	334- 337	Please clarify if laboratory instruments are expected to be in a state of IOQ for Phase I?
9	V. F. Laboratory Controls	339- 341	Guidance regarding expectations for the retention of API samples would be appreciated. Similarly, what are the expectations for retention of excipients?
9	V. G. Container Closure and Labeling	353- 355	Please identify requirements for containers for Phase I use. It is suggested that if not previously characterized, containers should be evaluated per USP <661> or other relevant criteria. To alleviate confusion this may need to be cited in brief (the sentence here discusses only package integrity/function).
9	V.H. Container, Closure And Labeling	365	Please also note: The reference is missing in the document for reference 5, on page 9 of this guidance.

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10	V.I.A Screening studies/micro dose Producers	387-391	No mention of the existing Manual for Policy and procedure map 6030.4 regarding "Screening INDs" is provided. It is suggested that a reference to this MaPP be provided in the draft guidance.
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