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March 17, 2006

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

Ref.: [Docket Number: **2005D-0286**]

Draft Guidance for Industry: INDs – Approaches to Complying with cGMP during Phase I

Dear Sir/Madam:

The Parenteral Drug Association (PDA) is pleased to provide these comments on the draft *Guidance for Industry, INDs – Approaches to Complying with cGMP during Phase I*. PDA is an international professional association consisting of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical manufacturing and quality. These comments were generated by a PDA Working Group that consisted of industry professionals from 10 different pharmaceutical and consulting firms, and included international representation.

Overall, we consider this document to be helpful guidance. We agree that required manufacturing controls vary with the stage of development; and that the industry has a responsibility to implement appropriate controls that consider the specific product and production situation and current process and product knowledge; in accordance with good scientific principles.

Attached, please find specific detailed suggestions regarding this draft guidance. In addition, our general suggestions are summarized below:

- The scope of Phase 1 studies should be more succinctly described. It should also be clarified that use of this guidance is appropriate for the manufacture of material to use for phase 1 studies, even if the development of the new product itself has progressed into later phases (e.g., repeating a Phase 1 study due to a dosage form change).
- The 1991 FDA Guideline on the *Preparation of Investigational New Drug Products (Human and Animal)* should remain in effect until a new Phase 2/3 guidance document is written.
- The concept of the implementation of appropriate quality control needs clarification. We suggest utilizing the concept of a quality system including suitable use of the terms Quality Unit, Quality Control and Quality Assurance.
- Although the same personnel may perform production and testing in smaller operations, we would suggest that separate personnel perform production and release operations.
- The expectation that this guidance applies to contract manufacturers and other "specialized facilities" such as academic institutions needs to be strengthened.

2005D-0286

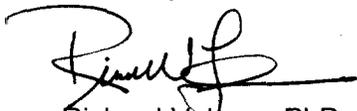
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- We appreciate the difficulty in clearly describing GMP requirements for all various types of production scenarios. To further ensure patient safety, however, we suggest that the guidance recommend that the need for additional controls for the manufacture of products under aseptic conditions be considered when more traditional filling lines are used to manufacture phase 1 materials.
- Requiring an "internal performance review" for bioprocesses is not appropriate for phase 1 materials given the fact that few lots are produced, frequent process changes are made, and each lot needs to be examined on a real-time basis to compare it to previous lots.

We would like to encourage the FDA to develop further guidance for phases 2 and 3 prior to the withdrawal of the 1991 FDA Guideline on the *Preparation of Investigational New Drug Products (Human and Animal)* in view of the fact that 21 CFR Parts 210 and 211, as written, are not appropriate requirements for phase 2 and 3. We also would encourage that concepts given in this guidance be incorporated into other related regulatory guidance documents to achieve worldwide harmonization on this topic (e.g., Annex 13 to Volume 4, Good Manufacturing Practices, ICH Q7A Section 19 – APIs for use in clinical trials). This is particularly important since many pharmaceutical companies are international companies producing materials for clinical trials throughout the world.

We appreciate the opportunity to comment on this guidance document as we both strive to develop guidance that facilitates the production of investigational new drugs while ensuring patient safety. Please contact us if we can be of any further assistance with the development of this important Guidance for Industry.

Sincerely,



Richard V. Levy, PhD
Vice President, Scientific and Regulatory Affairs
PDA

PDA Comments on draft FDA Guidance for Industry - Phase 1 GMPs

Compiled PDA WG Comments

Section	Line	Comment/Rationale	Suggested Change or Wording	Critical
I.	31	The Agency should qualify what is meant by "most investigational drugs" by referring to the explanation given in the Scope section of this document.	"This guidance is being issued concurrently with a direct final rule (and companion proposed rule), which specifies that the particular requirements in Part 211 (21 CFR 211) need not be met for most investigational drugs (see Scope section) manufactured for use during phase 1 development."	
II.	75	What is meant by "certain exploratory products"? Should use the same wording that is used in the Final Rule.	"As the new rule specifies, the particular requirements in Parts 211 (21 CFR 211) need not be met for certain exploratory products most investigational drugs (see Scope section) manufactured for use during phase 1 development."	X
II.	80 - 81	If the 1991 FDA Guideline for the Preparation of Investigational New Drug Products is eliminated when the phase 1 guidance for industry document is finalized, all portions of 210 and 211 could be considered applicable to phases 2 and 3. This would place undue burden on the industry. Therefore, we suggest that the 1991 guideline remain in effect until the new phase 2 and 3 guidance document is available.	"The 1991 Guideline on the Preparation of Investigational New Drug Product (Human and Animal) will continue to provide guidance for phase 2 and 3 production until further guidance is available through the Agency ⁴ ."	X
III	89	Change "investigational products" to "investigational drug products". Also, reword for clarity.	"The guidance applies to investigational drug products whether they are produced in small- or large-scale environments. Such studies are typically designated to assess tolerability or feasibility for further development of a specific drug or biological product."	
III	86 - 95	Clarify Scope (i.e., boundaries) of a Phase 1 study (e.g., purpose of study, types of subjects). This can be accomplished by adding a definition for Phase 1 studies.	Add definition to glossary for Phase 1 study. Refer to PDA comment for Glossary, line 599	
III	91	Suggest that the scope include Phase 1 type studies (e.g., PK studies) that are performed even if the IND has progressed into later phases (e.g., change in dosage form requiring phase 1 type studies to be repeated).	Add the following sentence: "Phase 1 studies to be performed on investigational new drugs (e.g., a new formulation requiring PK studies), even if the investigational new drug has progressed into later phases (e.g., phase 2), may be manufactured according to this guidance."	
V	134	Remove the examples. They are not needed and they add confusion. Appropriate warehousing is necessary to assure the integrity of investigational new drugs.	(e.g. those that address expiration dating 211.137(g), and warehousing 211.142)	
IV.	136	The Agency should qualify what is meant by "most investigational drugs" by referring to the explanation given in the Scope section of this document.	"...and are not relevant to the manufacture of most drugs for investigational use for phase 1 studies (see Scope section)."	
V.	158	The Agency should qualify what is meant by "most investigational drugs" by referring to the explanation given in the Scope section of this document.	"These recommendations are designed to provide approaches to cGMP that appropriately address factors associated with the production of clinical supplies for use in most phase 1 studies (see Scope section)."	

V.	159 - 171	Appear to be mixing together the concepts of analytical procedures, quality system procedures, and production procedures in this section. In addition, we should be thinking more in terms of a Quality System (see Section V.B.) rather than QC procedures.	<p>Recommend rewrite:</p> <p>"During product development, the integrity of investigational drug products for human use is maintained by an effective Quality System. Such a system facilitates suitable testing and control, the production of equivalent or comparable investigational product for further clinical studies, and the effective management of the changes that are expected during development. More specifically, a Quality System provides:</p> <ul style="list-style-type: none"> - Written procedures that are well defined - Appropriate utilization of risk management - Equipment that is appropriately controlled for the intended use - Accurate and consistently reported data - Maintenance of the integrity of clinical study materials"
V	170	Clarify meaning of "adequately controlled equipment" to indicate that it should be "calibrated and maintained".	<p>Change to:</p> <p>"- Equipment that is calibrated and maintained"</p>
V	175	Use of the phrase "appropriate standards of safety, identity, strength, quality, and purity" is less clear than utilization of the term "specifications", which is included in the glossary of this document.	"...to ensure that the investigational drug meets predefined specifications."
V	194-207	<p>Suggest clarifying that contract manufacturers must comply with the requirements of this guidance, as well.</p> <p>It should also be clarified that protecting the product from contamination is required (therefore, change "consider carefully the risks" to "minimize the risk").</p> <p>Suggest clarifying the guidance document by designating this as a separate section (i.e., underlining the sentence: "Use of specialized production facilities and testing laboratories (e.g., contract, academic institutions, clinical research units)").</p>	<p>Recommended rewrite:</p> <p><u>"Use of specialized production facilities and testing laboratories (e.g., contract, academic institutions, clinical research units)</u></p> <p>This guidance is applicable to contractors and other specialized service providers as well as the sponsor. The sponsor and contractor or service provider should minimize the risk from the production environment that might adversely affect the integrity of an investigational new product, especially when the investigational new product is produced in laboratory facilities that are not expressly or solely designed for that purpose. For example, of particular importance is ..."</p>
VB	224	Change "Quality Control Function" to "Quality System". "Quality Control" is the term that is generally associated with just the laboratory. The scope of this section should discuss the entire quality system that should be established.	"B. Quality System"

VB	226-238	<p>This section should discuss the quality system (including the establishment of written procedures) that should be established for the manufacture of phase 1 INDs. We do not recommend the introduction of a new term "QC Plan" to describe this system.</p> <p>Should add the requirement to examine raw materials.</p> <p>Corrective actions may not always be necessary.</p> <p>Complaints should also be investigated.</p>	<p>Recommended rewrite: "We recommend that every producer establish written procedures that address the following:</p> <ul style="list-style-type: none"> - Responsibility for examining the various components used in the production of a product (e.g., raw materials, containers, ... - Responsibility for review and approval of production procedures... - Responsibility for releasing or rejecting... - Responsibility for investigating and initiating corrective action, when required, if unexpected results or errors occur during production, or in response to complaints 	
VB	239-251	<p>"QC" in this context - lines# 239, 246 and 247 - should be "QA" (the referenced activity is not a laboratory function). "QA" in this context is the accepted industry term.</p> <p>Recommend moving sentence beginning at line 240 to later in the paragraph to allow the same theme (QA responsibilities) in line 245 to connect with the paragraph above.</p> <p>Believe the intent here is for very small operations (just a handful of people) in a research facility may not have the resource to have a separate QA function. Suggest clarifying this situation by including an example and by adding a footnote to reference the PET guidance document.</p> <p>A second independent person should release the batch.</p> <p>Analytical development personnel may also perform testing of clinical supplies (re., Q7A).</p>	<p>Recommend rewrite: "It is important to note that quality is the responsibility of all personnel involved in manufacturing. We also recommend that QA responsibilities be performed independently from production responsibilities. However, in limited circumstances, depending on the size and structure of an organization, all QA functions could be performed by the same individual (e.g., in a small research organization)ⁿ. For example, in some small operations, it may be justified to have the same individual perform both production and testing functions. We recommend, however, that another qualified individual not involved in the production operation perform the review of the production records and release of the batch.</p> <p>When activities such as testing, commonly performed by dedicated QC personnel in commercial manufacture, are performed by production or analytical development personnel, adequate controls should be in place (e.g., segregation of testing from production so as to not contaminate testing or negatively affect test results).</p>	X
VC	255	Suggest clarifying what "adequate" work areas and equipment might be based upon.	<p>Recommend rewrite: "Any facility, including a laboratory, used for production of investigational new drugs for phase 1 studies should have controls for the work areas and equipment related to the intended use of the product, minimizing risk for loss of product integrity."</p>	
VC	266	All MAJOR pieces of equipment should be identified, consistent with 21CFR 211 requirements.	"We recommend that all major pieces of equipment used for a particular process be identified and documented in the production record."	
VD	281	It is not necessary to include IMP batch number for the raw material. This should be in the batch record(s), not part of the receipt records.	".....component lot number, investigational product batch number, storage conditions..."	
VD	286-288	Justification for attributes and acceptance criteria should be documented.	"However, attributes and acceptance criteria selected for use in the specific investigational drug should be based on documented scientific knowledge and experience."	

VD	297	Identity testing should be performed on API received from outside the company, however, identity testing should not be required for intracompany shipments.	"For each batch of the drug substance (or API), we strongly recommend performing confirmatory identity testing when API is purchased from a supplier, regardless of whether documentation has been provided." For intra company shipments where unique tamper evident seals are used, confirmatory identity testing is not required.	
VE	305	The section relates to production only	"A record of in-process testing and production data that details the components, equipment, and procedures used."	
VF	322	The current proposed text implies some degree of validation of analytical test methods already in Phase 1, which would be an additional regulatory burden that is not necessary.	"Analytical tests used in production should be scientifically sound and appropriate for the intended use."	
VF	340	It is not always possible to allocate twice the amount of sample just for retain because of the small volumes produced.	"... we recommend that the sample consist of twice the a quantity adequate to perform additional testing if required later to confirm the identity or integrity of the product... necessary to conduct release testing... "	
F.1.	342-343	Logistics of maintaining samples until 2 years after the close of the IND are difficult and do not add value as the material does not represent what was used in the study and any questions about the material would have already surfaced. Change the sample retention requirement to also include the option to retain samples for 2 years past expiry of the material (e.g., 5 year expiry plus 2 years = 7 years).	"We recommend that the samples be appropriately stored and retained for at least 2 years following study termination or 2 years beyond product expiration (e.g., 5 year expiry plus 2 years)."	
H	361-362	Distribution to subjects is a GCP responsibility. This is tracked by clinical trial monitors and not by the developers, manufacturers and controllers of the IMPs. Eliminate the requirement that the distribution to the subjects is a GMP responsibility.	"As it relates to phase 1 trials, the term distribution includes the transport of an investigational new product covered by this guidance to clinical investigators."	X
VI	374	Need to specify the records that are produced.	"Quality system records"	
VI.B.	427-429	If any issues arise from multi-product facilities, a deviation would be automatically raised, requiring a review of the controls in the area. Therefore, a periodic assessment of the controls is not needed.	Delete the requirement to perform a periodic assessment.	
VI.C.4	498	During Phase 1, it is unlikely that multiple batches of the same investigational product will be made utilizing a consistent manufacturing process. In addition, there should be an on-going program to assess the consistency of the material produced (e.g., impurity profile), therefore, there would not be any value derived from assessing the "control and consistency of the production process" after multiple lots are manufactured.	Delete requirement to perform an internal performance review when multiple batches of the same investigational product are made.	
VI.D.	537	Considering the criticality of assuring product sterility, personnel performing aseptic techniques should be qualified.	"Training personnel using aseptic techniques and qualifying them in those techniques."	
VI.D.	553	Recommend adding a requirement to consider taking additional precautions when utilizing traditional aseptic filling facilities (e.g., environmental monitoring, equipment qualification).	Add the following: "Consideration should be given to any additional controls that may be needed when utilizing a traditional filling line (e.g., environmental monitoring, media fills, equipment qualification)."	
VIID	521	Sometimes the manufacture of Phase 1 products may be done only once and validation should not be required. Therefore, it should be clarified that smoke studies are not required.	"Ensuring that items within a laminar airflow aseptic workstation do not interrupt the airflow (the use of smoke studies are not required)."	
References	633	Add reference 5 to exploratory IND studies (mentioned in line 389).	Reference 5 is missing.	

Glossary		A number of terms such as "Specification" and "Quality Unit" appear in the Glossary, but not in the body of the document.	Keep the terms in the glossary if they are used in the document, otherwise, remove them from the glossary.	
Glossary		The definition of "Component" does not match the description given in lines 229 - 231.	Align definitions.	
Glossary	599	Define Phase I study	Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. Phase 1 studies also evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans. The total number of subjects included in Phase 1 studies is generally in the range of twenty to eighty. [FDA website]	
Glossary	616-618	Include the responsibilities of Quality Assurance unit in the Quality Units definition. Distinguish between QA and QC.	Quality Control - Checking or testing that specifications are met. [Q7A] Quality Assurance - The organizational unit, separate from production operations, charged with the responsibility to oversee the establishment and operation of an appropriate quality system as well as the proper disposition of manufactured items. [proposed definition]	
Glossary		Recommend the addition of a "Quality System" definition.	Quality System - Business practices that define the organizational structure, processes, and procedures needed to fulfill product/service requirements, regulatory requirements, and achieve customer satisfaction. [proposed definition]	