



Date: MAR 20 2006

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Re: Docket No. 2005D-0286  
Response to FDA Call for Comments:  
Draft Guidance for Industry on Investigational New Drugs: Approaches to  
Complying with Current Good Manufacturing Practice During Phase 1

Dear Sir or Madam:

Reference is made to the January 17, 2006 Federal Register Notice requesting comments on the FDA's Draft Guidance for Industry on Investigational New Drugs: Approaches to Complying with Current Good Manufacturing Practice During Phase 1.

AstraZeneca welcomes the opportunity to comment on this important new guidance. We strongly support the Agency in preparing guidance for interpretation and application of GMP for early Phase 1 studies and welcome the recognition that the requirements in 21 CFR 210 and 211 are not appropriate for these early studies.

AstraZeneca has reviewed this draft guidance and our comments are attached.

Please direct any questions, or requests for additional information to me at (302) 886-5895.

Sincerely,

A handwritten signature in black ink, appearing to read 'B. Sickels', written in a cursive style.

Barry D. Sickels, Executive Director  
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**US Regulatory Affairs**

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**Submission of Comments to FDA (Docket 2005D-0286 INDs; Approaches to Complying with CGMP During Phase I)**

**FINAL DRAFT 6<sup>th</sup> MARCH 2006**

**General comments**

AstraZeneca welcomes the opportunity to comment on this important new guidance from FDA and is pleased to provide general comments in this section and more detailed, specific comments below.

We strongly support the Agency in preparing guidance for application and interpretation of GMP for early Phase I studies and welcome the recognition that the requirements of the Regulations as defined in CFR Parts 210 and 211 are not appropriate for these early studies.

Comments:

- We request that the Agency commit to further providing guidance for products destined to Phase 2 and Phase 3 clinical studies. We suggest that without such commitment the expectation would be that the requirements of CFR Part 210 and 211 would be required. Although it is stated as a footnote in the background that the Agency is considering additional guidance, we would strongly recommend that this commitment is made.
- Until the additional guidance for Phase 2 and 3 is issued, we suggest that the current 1991 Guideline on the Preparation of Investigational New Drug Products (Human and Animal) remains in effect to avoid the expectation that the full requirements of CFR Parts 210 and 211 would be applied.
- The scope should be clarified to require that the guidance for use in Phase I studies is appropriate even when the development of the NCE has progressed into later stages e.g. repeating a Phase I study when there is a formulation change.
- The concept of a defined Quality System, incorporating both Quality Control and Quality Assurance roles, should be included. Historically, the role of the Quality Unit has evolved into both Quality Assurance and Quality Control activities and it is suggested that the Agency include this concept into this guide in line with current thinking in the development and application of ICH Q10 and Q7A.
- The expectation that this guidance applies to contract manufacturers and other “specialised facilities” such as academic institutions should be strengthened.
- We request the Agency to use the opportunity to harmonise with other international requirements of GMP for clinical studies e.g. EU Annex 13.

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<b>Specific comments</b>			
Section and line	Critical comment	Comment and rationale	Proposed rewording (if applicable)
I, 17		The Agency should use consistent wording when describing who the guideline is intended for.	"Manufacturers of investigational drugs" should be used throughout.
I, 22		The Agency should incorporate "Quality System" principles rather than quality control (QC) principles	Use "applying "Quality System" principles.
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	<b>C</b>	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 <del>certain exploratory products</del> most investigational drugs (see Scope section) manufactured for use during phase 1 development."
II, 80-81	<b>C</b>	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.	" <i>The 1991 Guideline on the Preparation of Investigational New Drug Product (Human and Animal)</i> will continue to provide guidance for phase 2 and 3 production until further guidance is available through the Agency."
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.
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."

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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."
IV, 134		Remove the examples. They are not needed and they add confusion. Appropriate warehousing is necessary to assure the integrity of investigational new drugs.	<del>(e.g. those that address expiration dating 211.137(g), and warehousing 211.142)</del>
IV, 135		Clarify what "most investigation drugs " means.	Provide explanation of what most investigational drugs are by referencing the Scope section as stated for I, 35 above. Re word as: "are not relevant to the manufacture of most investigational drugs (see Scope section) for investigational use for phase 1 studies".
V, 158		The Agency should qualify what is meant by "most phase I studies" 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		We support the intention of this section but it appears 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.	Recommend rewrite: "During product development, the integrity of investigational drug products for human use are 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: <ul style="list-style-type: none"> <li>- Written procedures that are well defined</li> <li>- Appropriate utilisation of risk management</li> <li>- Systems for releasing and rejecting starting materials, component and investigational drugs</li> <li>- Equipment that is appropriately controlled for the intended use</li> <li>- Accurate and consistently reported data</li> <li>- Maintenance of the integrity of clinical study materials"</li> </ul>
V, 170		Clarify meaning of "adequately controlled equipment" to indicate that it should be "calibrated and maintained".	Change to: "- Equipment that is calibrated and maintained"
V, 175		Use of the phrase "appropriate standards of safety, identity, strength, quality, and purity" is less clear than utilization of the	"...to ensure that the investigational drug meets predefined specifications."

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		term "specifications", which is included in the glossary of this document.	
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:                  "This guidance is applicable to all manufacturers of investigational drugs, including contractors and other specialized service providers. The manufacturer 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 made in laboratory facilities that are not expressly or solely designed for that purpose".</p>
VB, 224		<p>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.</p>	"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 addresses the following:</p> <ul style="list-style-type: none"> <li>- Responsibility for examining the various components used in the production of a product (e.g., raw materials, containers, ...</li> <li>- Responsibility for review and approval of production procedures...</li> <li>- Responsibility for releasing or rejecting...</li> <li>- Responsibility for investigating and initiating corrective action, when required, if unexpected results or errors occur during production, or in response to complaints</li> </ul>
VB, 239-251	<b>C</b>	<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>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 organisation, all QA functions could be performed by the same individual (e.g., in a small research organisation)<sup>n</sup>. For example, in</p>

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		<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>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>
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 and not ALL equipment.	"We recommend that all major pieces of equipment used for a particular process be identified and documented in the production record."
VD, 273		Description of component is not consistent with definition in Glossary, line 572	Align definitions throughout.
VD, 281		It does not make sense 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, <del>investigational product batch number,</del> 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 and should not be required for intra company 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, laboratory requirements should be in a different section.	"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	"Analytical tests used in production should be scientifically sound and

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		of analytical test methods already in Phase 1, which would be an additional regulatory burden that is not necessary.	appropriate for the intended use."
VF, 339		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 <del>twice the</del> a quantity adequate to perform additional testing if required later to confirm the identity or integrity of the product... <del>necessary to conduct release testing...</del> "
VF.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)."
VH, 361-362	<b>C</b>	Distribution to subjects is a GCP responsibility. This is tracked by clinical trial monitors and not by the developers, manufacturers and controllers of the investigational drug. Delete the requirement in the guide that 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."
VI, 374		The bullet point <ul style="list-style-type: none"> <li>All quality control function" is vague and recommend it is deleted.</li> </ul>	Delete " all quality control function"
VI.B, 427-429		If any issues arise from multi-product facilities, an investigation would be undertaken and so the effectiveness of the controls in that area would automatically be reviewed. 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 utilising 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/521		Sometimes the manufacture of Phase 1 products may be	"Ensure that items within a laminar airflow aseptic workstation do not

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		done only once and validation should not be required. It is implicit that demonstration of interruption to airflow usually requires use of smoke studies, these would not be appropriate for single batch manufactures, Therefore, it should be clarified that smoke studies are not required in these cases.	interrupt the airflow. This may be assessed by review of other similar manufactures and the use of smoke studies is not required."
Glossary, 572		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 organisational 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 organisational structure, processes, and procedures needed to fulfil product/service requirements, regulatory requirements, and achieve customer satisfaction. [proposed definition]
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.
References		Add reference 5 to exploratory IND studies (mentioned in line 389).	Reference 5 is missing.