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March 7, 2006

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

Re: Draft Guidance for Industry on Investigational New Drugs; Approaches to Complying with Current Good Manufacturing Practice During Phase 1 [Docket 2005D-0286, 71 *Federal Register*, No. 10, pages 2552-2554 (January 17, 2006)]

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA companies are leading the way in the search for new cures. PhRMA members alone invested an estimated \$39.4 billion in 2005 in discovering and developing new medicines. Industry-wide research and investment reached a record \$51.3 billion in 2005.

We appreciate the opportunity to provide comments on the subject draft guidance, and we thank you in advance for your consideration of them as you finalize the guidance.

Sincerely,

Alice E. Till, Ph.D.

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*Pharmaceutical Research and Manufacturers of America*

## **PhRMA's Comments on FDA Draft Guidance for Industry on Investigational New Drugs: Approaches to Complying with CGMP During Phase 1**

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### *General Comments*

PhRMA strongly supports the development of this FDA guideline, as we believe there is currently a general consensus within Industry that there should be an incremental application of CGMP expectations throughout clinical development as a product approaches commercialization. It is critical however, that once finalized and implemented, additional FDA guidance should be issued regarding the CGMP expectations for production and testing of phase 2 and 3 clinical supplies. Without proper guidance on this topic, there is a high probability that the phase 1 CGMP guidance will be incorrectly interpreted that there is no differentiation between the commercial CGMP expectations (specified in Parts 210 and 211) and the phase 2 and 3 CGMP requirements. It will cause an undue burden on Industry to follow all of the commercial CGMP expectations during the later phases of clinical development where product and process knowledge is still evolving and there is still limited manufacturing experience (e.g. requiring complete process and method validation in phase 2 when the commercial, synthetic/formulation process and analytical methods have not been finalized).

Patient safety remains the central focus for sponsors of clinical studies regardless of the phase of clinical development. We believe that throughout drug development, the basic principles of CGMP must apply, namely:

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

In addition to providing guidance on the incremental CGMP requirements as the clinical phase progresses, we recommend that additional clarification should be added to the draft phase 1 CGMP guidance on these specific areas (details of these concerns are listed in the relevant section(s) on the line specific comments):

- Consistently defining and applying to whom the guidance is addressed. The current draft offers a variety of addressees, e.g., "persons.... producing investigational drugs", sponsors, contractors, commercial manufacturers. We understand that the guidance is directed to "manufacturers of investigational drugs", and this includes all those that manufacture such drugs for sponsors wanting to perform clinical studies under an IND.
- Consistently defining and applying specific concepts and terms used throughout the guidance (e.g., Quality Unit / Quality Control / Quality Assurance). This guidance frequently refers to the term "Quality Control or QC" which is often defined in other guidances as sampling, testing and inspection. This concept needs to be expanded to include quality assurance and quality systems in line with current thinking in the development and application of ICH Q10 and Q7A
- Clearly specifying in the guidance what is not required for phase 1 CGMPs (e.g. during phase 1 formal specifications not required and analytical methods do not need to be fully validated to the extent required by ICH Q2A/B).

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- Avoiding vague terminology and phrases such as “most drugs” or “most phase 1 studies” and instead including examples of exceptions. Details of these concerns are listed in the section on line specific comments.
- Aligning the CGMP expectations outlined in this draft guidance with other FDA draft guidances as they are finalized, notably *Analytical Procedures and Methods Validation Chemistry, Manufacturing, and Controls Documentation* (August 2000) and *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations* (September 2004), which already include some recommendations with respect to clinical phase expectations.
- Harmonizing this draft guidance with existing international guidances such as ICH Q7A applying to Investigational substances and ICH Q9, EC Annex 13, and EMEA CHMP/QWP/185401/2004. Without additional harmonization, organizations that execute multinational clinical investigations may receive little increased flexibility suggested by this phase 1 CGMP draft guidance.

Finally, few manufacturing facilities for investigational products restrict production to phase 1 materials alone. Often the material used to initiate phase 1 studies is used in phase 2 evaluations. With this guidance and the withdrawal of Parts 210 and 211 being applicable to phase 1 material only, this requires production of additional material under different and more stringent CGMP standards (e.g. phase 2), and thus could be an unnecessary economic burden and result in delays in drug development. Thus from a practical viewpoint, this draft guidance appears to provide value to a limited subset of manufacturers only, with perhaps most of the relief going to academic organizations such as NCI or NIH. Consequently, we encourage the Agency to develop guidance for CGMP for later phases of clinical development as a priority.

**Line Specific Comments**

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|------|--------------------|---------|---|
| 1    | I.<br>Introduction | 17      | The guidance should clearly state that it is directed to “manufacturers of investigational drugs”. As currently drafted, it is not.   |
| 1    | I.<br>Introduction | 22      | In line with our general comment regarding expansion of the Quality Control concept, we recommend rewording from “... applying quality control (QC) principles” to “...applying quality system principles as outlined below...”. Please refer to the comments in line 162 to 171 for further explanation. |
| 1    | I.<br>Introduction | 31      | What is meant by “most investigational drugs”? Does the agency have any specific exceptions in mind? If so, these need to be specified. If not, then the word “most” should be deleted.   |
| 2    | II.<br>Background  | 68      | Currently, footnote 4 on the bottom of page 2 hints to the possibility of additional FDA guidance in the future regarding phase 2 and 3 CGMP expectations. We suggest that this statement should be moved up into the body of the text (as a  |

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|      |                   |         | <p>supplemental last sentence in line 68) to clearly specify the Agency is planning to issue additional guidance and/or regulations on this topic (which further supports the Agency's expectations for the application of phase dependent CGMPs).</p> <p>The new sentence could be re-phrased to read: "To reinforce the Agency's expectations for the incremental application of CGMPs during clinical development, we are planning on developing additional guidance and/or regulations to define the CGMP requirements when producing investigational drugs for phase 2 and phase 3 clinical studies".</p> |
| 2    | II.<br>Background | 75      | Please explain what is meant by "certain exploratory products". Again, if the Agency has specific exceptions in mind, these should be specified, or the word "certain" should be deleted.  |
| 3    | II.<br>Background | 80 - 81 | "Phase 2 and 3 production will continue to be subject to those portions of 210 and 211 that are applicable." More 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. This statement does not align with the incremental CGMP approach mentioned earlier in this section. We request that the Agency be more specific on the sections of 210 and 211 which are applicable and those which are not.   |
| 3    | III.<br>Scope     | 86      | Please clarify if the Agency is intending this phase 1 CGMP guidance to apply only to the phase 1 CGMP expectations for drug products or to both drug substances and drug products.  |
| 3    | III.<br>Scope     | 100-101 | Please clarify the Agency's expectations for Combination Products (drug/devices).  |
| 3    | III.<br>Scope     | 102     | Investigational materials may be produced in sufficient quantity to allow use in phase 2 or even phase 3 (e.g., highly potent drug substances). Restricting the use of investigational materials produced under the degree of CGMP outlined in this guidance only to phase 1 clinical studies would increase costs and extend development times. Consequently, we recommend clarifying this bullet with "Investigational new drugs manufactured for phase 2 and 3 studies (but the Agency may consider exceptions in justifiable cases such as highly potent compounds)".                                      |

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| 4    | IV.<br>Statutory and<br>Regulatory<br>Requirements         | 135-136 | What is meant by "most drugs"? If the Agency has specific exceptions in mind, these should be stated, or the word "most" should be deleted.  |
| 4-5  | V.<br>Recommendations<br>for Complying<br>with the Statute | 158-159 | What is meant by "most phase 1 studies"? If the Agency has specific exceptions in mind, these should be stated, or the word "most" should be deleted.  |
| 5    | V.<br>Recommendations<br>for Complying<br>with the Statute | 162-171 | <p>PhRMA supports the Agency's intent with this section, but we believe some clarification would be helpful, especially for those institutions that may be less familiar with the overall principles of CGMP. In addition we believe closer alignment to the requirements in ICH Guideline Q7A and other non-US agencies would be beneficial for the multinational companies. Therefore we offer the following alternative for consideration by the Agency:</p> <p>"During product development, the quality and safety of the investigational drug products are maintained, in part, by having appropriate quality oversight and testing procedures in effect. This can be achieved by establishing an effective Quality System. Such a system will also facilitate the production of equivalent or comparable investigational product for further clinical study as needed, and will allow the effective management of the changes that are expected during development.</p> <p>More specifically, a Quality System will include:</p> <ul style="list-style-type: none"> <li>• Written procedures that are well defined</li> <li>• A system for risk management</li> <li>• Equipment that is controlled appropriately for the intended use</li> <li>• A system for appropriate sampling, inspecting, and testing components, intermediates, bulk, and packaged product</li> <li>• A system for approval or rejection of each batch of material</li> <li>• Accurate and consistently reported data, and maintenance of records</li> <li>• Maintenance of the integrity of clinical study materials" </li></ul> |
| 6    | V.<br>Recommendations                                      | 205     | The draft guidance recommends "A formal evaluation of the production environment to identify potential hazards". More  |

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|      | for Complying with the Statute                    |         | <p>clarity is needed on the intention of this recommendation. While most manufacturers perform this evaluation, it is not necessarily recorded in a single written document, particularly at phase 1. The recommendation appears to increase the regulatory burden by specifically setting this expectation.</p> <p>This bullet point should be revised to read: "The production environment should minimize potential hazards that could impact product quality and safety".</p>  |
| 6    | V. Recommendations for Complying with the Statute | 211-214 | <p>More clarity is needed on the intention of the recommendation: "Producers should establish production controls based on a risk assessment for the product and manufacturing process and follow good scientific and quality control principles when implementing specific practices and procedures for CGMP." Does the Agency intend to recommend the creation of a formal risk assessment document for each product and manufacturing process? We do not feel this is necessary for investigational products and suggest deleting "establish production controls based on a risk assessment for the product and manufacturing process and follow good scientific and quality control principles when implementing specific practices and procedures for CGMP". Instead we recommend replacing this line with "Producers should follow good scientific and quality assurance principles when implementing specific practices and procedures for CGMP".</p> |
| 6    | V. A. Personnel                                   | 220     | <p>The same comments regarding redefining the term "QC" apply here as well especially to those job functions which require a thorough knowledge of quality principles and systems. We recommend replacing "QC" with "Quality".</p>   |
| 6-7  | V. B. Quality Control Function                    | 224-251 | <p>PhRMA is in full agreement with the Agency with respect to assuring the quality of investigational products. However, we believe that some clarification and differentiation, consistent with ICH Q7A which applies to investigational materials, between overall quality oversight, Quality Control (sampling, inspection and testing), and product release would be helpful, especially for institutions that have less experience with commercial production. We believe we can strengthen the Agency's intent by bringing the discussion on the responsibility for quality to the front of the section. PhRMA therefore offers the following alternative wording for Section V. B. for the Agency's consideration:</p>  |

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|      |         |         | <p data-bbox="672 310 846 342">"B. Quality</p> <p data-bbox="672 373 1442 821">Quality is the responsibility of all personnel involved in the manufacturing, packaging, and testing of investigational products. Nevertheless, we recommend that final responsibility for quality oversight and approval or rejection of each batch of product for use in clinical trials should be assigned to a designated individual or function. In keeping with the basic principles of CGMP, this individual or function must be independent from production. An exception may be made where this separation may not be practical, in which case accountability for release and quality oversight must be clearly defined; and additional, periodic review of production records should be carried out by an independent, appropriately qualified individual.</p> <p data-bbox="672 856 1442 957">We recommend that every producer establish a written Quality System. For example, a sound Quality System should provide for the following functions:</p> <ul data-bbox="727 968 1446 1661" style="list-style-type: none"> <li data-bbox="727 968 1446 1199">• Establishing, reviewing, and approving 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 (starting materials, primary packaging materials, labeling), intermediates and for the bulk and packaged product</li> <li data-bbox="727 1209 1446 1272">• Establishing, reviewing, and approving production procedures and test procedures</li> <li data-bbox="727 1283 1446 1377">• Responsibility for sampling, inspection, and testing of components, intermediates, and product. These activities are frequently defined as "Quality Control".</li> <li data-bbox="727 1388 1446 1524">• Responsibility for releasing or rejecting each clinical trial batch based upon a cumulative review of completed production records, test results, compliance with acceptance criteria, and other relevant information</li> <li data-bbox="727 1535 1446 1661">• Responsibility for appropriate investigation as well as ensuring any necessary corrective action, in the event that unexpected results or errors occur during production, testing, or in response to complaints.</li> </ul> <p data-bbox="672 1696 1442 1902">In order to avoid potential contamination of investigational product with laboratory reagents, we recommend that testing activities be separated from production activities. Ideally this can be achieved by use of separate rooms, but in some cases, for example with highly potent or radio-labeled materials, this may be accomplished through an appropriate physical means</p> |

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|      |  |         | of segregation within the room.”   |
| 7    | V. D.<br>Control of<br>Components        | 273     | The description of component in various parts of this guidance and relative to the requirements of section V. D. does not align with the definition of component in the Glossary (e.g. line 229 and line 572).   |
| 7    | V. D.<br>Control of<br>Components        | 279-282 | Recording of components 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:<br><br>“Records concerning an investigational product must contain or cross-reference relevant information on all components used during its manufacture. Information about components would include receipt date, quantity of the shipment, supplier’s name, component lot number, storage conditions and corresponding expiration or retest date.” |
| 8    | V. D.<br>Control of<br>Components        | 294-296 | If taken literally, the sentence “ ...testing for the incomplete attribute of the component is recommended” implies that all possible attributes may need to be tested, either by vendor or internally. It is suggested that that the end of the sentence should include “...unless that attribute is deemed and documented as scientifically irrelevant to the phase I nature of the formulation and/or investigation.”   |
| 8    | V. D.<br>Control of<br>Components        | 296-298 | Identity testing should be performed on API received from outside the company, however, identity testing should not be required for intracompany shipments.<br><br>Suggested rewording:<br><br>“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 appropriate controls are used (e.g. unique tamper evident seals), confirmatory identity testing is not required if the integrity of the shipment is intact.”     |
| 8    | V. E.<br>Production and<br>Documentation | 305-309 | This section addresses production, not laboratory testing.<br><br>This sentence should be revised to read: “A record of production data that details the components, equipment and   |

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|      |                                 |         | procedures used.”   |
| 8    | V. F.<br>Laboratory<br>Controls | 322-325 | <p>The term “reproducible” has a specific connotation in ICH Q2A/B for commercial testing and we recommend that this term be replaced. Also, in order to capture the intent of the language in line 305, we suggest rephrasing the paragraph starting at line 322 to read:</p> <p>“We recommend that testing should be performed under controlled conditions and follow written procedures describing the testing methodology and documentation of equipment used and results obtained. Analytical tests that provide information to support batch release (e.g. testing of components, in-process material, packaging, drug product) should be scientifically sound (e.g., specific, sensitive, and accurate) and suitable for the specified purpose.”</p>   |
| 9    | V. F.<br>Laboratory<br>Controls | 339-341 | <p>What are the Agency’s expectations for retaining API and excipient samples? For additional clarification, the following sentence should be revised: “When feasible, we recommend that the sample consist of twice the quantity necessary to conduct release testing (excluding any testing for pyrogenicity and sterility).”</p> <p>The revised sentence should read: “We recommend that the sample consist of a quantity adequate to perform additional testing or investigation if required later (e.g. two times the quantity required for release testing). It is not always possible to allocate twice the amount of samples just for retain samples, particularly for products that are highly individualized (e.g. anti-idiotypic antibody to a individual specific B cell idiotypic).”</p> |
| 9    | V. F.<br>Laboratory<br>Controls | 341-343 | <p>The logistics of maintaining samples until 2 years after the close of the IND are difficult. In addition, this practice does not add value as the samples at the end of that period do not represent what was used in the study and any questions about the material would have already surfaced. In addition we find the value of storing the sample more than a year after the study close adds no value of the same reason. The close of the IND would also always occur at the earliest at the same time as the study is terminated and reference to the close of the IND is therefore unnecessary.</p> <p>We suggest the following modification:</p>  |

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|      |  |         | "We recommend that the samples be appropriately stored and retained for at least 1 year following study termination."  |
| 9    | V. F.<br>Laboratory<br>Controls                          | 347     | <p>The stability study should be designed appropriately to support the expected storage of the product.</p> <p>The revised sentence could read: "We recommend that sponsors initiate an appropriate stability study using representative samples of investigational new drugs ..."</p>   |
| 9    | V. I.<br>Recordkeeping                                   | 374     | The bullet point "All quality control functions" is vague and redundant to lines 369-370. We recommend deletion of this bullet.  |
| 11   | VI. B.<br>Multi-Product<br>Facilities                    | 426-427 | <p>For clarification, we recommend modifying the sentence to read:</p> <p>"Examples of appropriate controls include procedures for clearing the room of previous product materials, product segregation, component segregation, and use of unique identifiers".</p>  |
| 11   | VI. B.<br>Multi-Product<br>Facilities                    | 427-429 | <p>"Assessed" may imply testing, which may not be necessary. We suggest the following instead:</p> <p>"We recommend the implemented controls be reviewed periodically to evaluate their effectiveness."</p>  |
| 11   | VI. C.<br>Biological and<br>Biotechnological<br>Products | 458     | <p>The statement "...and clearance of substances" is unclear. We recommend re-phrasing the sentence to clarify the intent as meaning clearance of substances that are toxic in nature.</p> <p>We suggest the following instead:</p> <p>"...and clearance of substances that are toxic in nature (e.g., antibiotics, chemicals) be used in production and that adventitious agent testing be established as appropriate."</p>   |
| 12   | VI. C.<br>Biological and<br>Biotechnological<br>Products | 498-499 | We recommend that FDA eliminate any recommendation for documented periodic review in this guidance. Current IND regulations (21CFR312.33) require annual reports be made to the Agency, but a periodic quality review is not a statutory requirement until commercial product approval (21CFR211.180(e)). While most commercial manufacturers perform this type of evaluation as part of process development, requiring a separate report for analysis of phase 1 production increases burden to the industry. Further, there is no evidence |

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|      |   |         | that this will increase the safety of investigational products and assist the Agency in fulfilling its mission to protect the public health.  |
| 13   | VI. D.<br>Sterile Products/<br>Aseptically<br>Processed<br>Products | 518-519 | 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.<br><br>We recommend the following amendment:<br>"Disinfecting the entire aseptic workstations and monitoring of environmental conditions as appropriate (e.g. before aseptic manipulation, or between different operations during the same day)."  |
| 13   | VI. D.<br>Sterile Products/<br>Aseptically<br>Processed<br>Products | 531-532 | We have a concern that the proposed guidance does not fully address the sterilization of the investigational product. We therefore recommend inserting the following clarification:<br><br>"Documenting and following all procedures intended to maintain the sterility of the components, in-process materials, and final product (e.g. qualification of terminal or alternative sterilization procedures, media run qualifications for aseptic filling, etc.)." |
| 13   | VI. D.<br>Sterile Products/<br>Aseptically<br>Processed<br>Products | 533     | The term "test article" should be replaced with a more descriptive term such as "API" or "drug substance" to minimize confusion on the intention of this sentence (e.g. the term "test article" is frequently used in GLP applications and can imply a drug substance or product depending on the situation).   |
| 13   | VI. D.<br>Sterile Products/<br>Aseptically<br>Processed<br>Products | 543     | The same comments regarding redefining the term "QC" apply here as well. We recommend replacing "QC" with "Quality".  |
| 15   | Glossary  | 555     | We propose incorporating the following additions to the Glossary:<br><br><ul style="list-style-type: none"> <li>- Define adventitious agents</li> <li>- Define Quality System</li> </ul>  |
| 15   | Glossary  | 572-573 | The definition of "Component" does not match the description given in the body of the document in lines 229-231. The definition needs to include packaging commodities and clarify if it includes API raw materials. An alternate to the term   |

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|      |            |         | "ingredient" in the definition could be "material".   |
| 15   | Glossary   | 594-597 | This definition for "Microdose studies" is redundant to the text provided in lines 393-396, and we recommend that these definitions occur only once in the guidance.                |
| 16   | Glossary   | 601     | A comma is missing between the word "labeling" and "laboratory".  |
| 16   | Glossary   | 604-606 | This definition for "Screening study" is redundant to the text provided in lines 387-391, and we recommend that these definitions occur only once in the guidance.                  |
| 16   | Glossary   | 616     | It may be more appropriate to define the term 'Quality System' rather than "Quality Unit", which has been used in PhRMA's suggested text for Section V.B.                           |
| 17   | References | 633     | The reference mentioned in line 389 is missing in the References section. We recommend adding reference 5 on FDA guidance on <i>Exploratory IND Studies</i> to the References list. |