

## Overall Assessment of FDA Guidance on CGMPs During Phase 1 (Draft) Guidance:

Schering-Plough fully supports FDA's development and issuance of this guidance. We strongly agree that CGMPs should be applied to investigational drug products in clinical development with the understanding that controls will vary depending on the degree of product and process knowledge and experience gained as the product progresses through development from Phase 1 to 3 and ultimately to commercialization. General comments on this guidance and overall application of CGMPs throughout development are listed below:

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- It is critical that in parallel to finalizing this guidance, FDA issue additional guidance on their expectations of CGMPs for Phase 2 and Phase 3. Without this, there may be an unnecessary application of commercial CGMPs to Phase 2 and 3 of clinical development causing increased regulatory burden on pharmaceutical industry thereby increasing development time and overall costs. Another concern is that there may be an incorrect interpretation and application of Phase 1 CGMP principles to later phases of clinical development thus leading to a mismatch of FDA and industry expectations around CGMPs in Phase 2 and 3.

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- We encourage FDA to encourage other regions (e.g., European Union) on a similar phased approach to application of CGMPs during clinical development. Harmonization of this draft guidance with other existing international guidances such as EC Annex 13, and EMEA CHMP/QWP/185401/2004 would allow organizations the ability to take full advantage of the flexibility suggested by this Phase 1 guidance for multinational clinical trials.

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- As patient safety is a critical focus in clinical development, we recommend that the guidance be revised to assure that separate personnel perform production and disposition of the investigational drug product regardless of size of the company.

- The scope of Phase 1 studies should be more clearly described. The guidance should avoid vague terminology and phrases such as "most drugs" or "most studies" and instead should include examples of exceptions. We also recommend the Agency consider expanding the scope of this Phase 1 guidance to include Phase 1 studies being evaluated for exploratory pharmacokinetic (PK) assessment (e.g., PK assessment of new formulation) even if the drug product has moved into later phases of clinical development.

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- Specific areas of the guidance that require clarification are related to terminology of the Quality Unit vs. Quality Control vs. Quality Assurance. The guidance often uses the term QC, which is defined in other guidances as sampling, testing, and inspection. The role should be clarified to more appropriate terminology such as Quality Unit or Quality Assurance in line with current thinking in the development and application of ICH Q10 and ICH Q7A. Specific recommended revisions are included in the detailed comments listed below.

- The FDA should consider commenting on how inspectors will be trained on the concepts of this new guidance and expectations around inspections to ensure consistent interpretation.

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INDs—APPROACHES TO COMPLYING WITH CGMP DURING PHASE 1 (DRAFT)

Page	Section/Line	Response
1	I. Introduction/22	In line with our general comments regarding clarification of the Quality Control concept, we recommend rewording from "applying Quality Control (QC) principles" to "applying GMP principles." Deleted: ". Deleted: ".
2	II. 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. Deleted: ". Deleted: ".
3	III. Scope/89	Change "investigational products" to "investigational drug products." Also wherever "drug" or "product" is used alone to "mean investigational drug product," change to read "investigational drug product."
3	III. Scope/70-76 and 91	The guidance suggests that certain exploratory PK studies are within scope of this guidance. However the Agency should consider expanding the scope of Phase 1 studies being conducted for further PK exploratory assessment even if the investigational drug product has moved into Phase 2 and Phase 3. An example would be if a PK study was being conducted on a new formulation from that being evaluated in later phases of development. Suggest the following sentence be added: "Phase 1 studies to be performed on investigational formulation requiring PK studies), even if the investigational new drug has progressed into later phases of development and manufactured according to the requirements in this guidance." Deleted: s Deleted: e.g.
4	IV. Statutory and Regulatory 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.
5	V. Recommendations for Complying with the Statute/158-159	The intent of the word "Most" in most Phase 1 studies should be addressed. If the Agency has specific exceptions in mind, they should be defined.
5	V. Recommendations for Complying with the Statute/170	Clarify meaning of "Equipment that is adequately controlled." A proposed revision is as follows: "Equipment that is adequately controlled for its intended use." Deleted: ". Deleted: ".

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5	V. Recommendations for Complying with the Statute/159-171	<p>It appears the guidance is mixing together the concepts of analytical procedures, quality system procedures in this section. In addition, it may be more clear to focus and clarify the discussion around the Agency's terminology related to quality framework rather than QC procedures. As stated, the Agency highlights that the recommendations in the guidance will help provide an appropriate quality framework for a variety of investigational drugs manufactured in various situations. Describing this framework fully and early in the guidance will be helpful especially for institutions and smaller companies that may be less familiar with the overall principles of CGMP. The following section could be revised as such:</p> <p>“B. <u>Quality Framework</u></p> <p>During <u>drug product</u> development, the quality and safety of investigational drug products are ensured by having appropriate quality assurance oversight and by having appropriate testing procedures in place. Having an effective quality framework in place. This framework containing the establishment of standard procedures will facilitate the production of equivalent or comparable investigational <u>drug product</u> for further development. The following is an example of elements that can be included in this framework:</p> <ul style="list-style-type: none"> <li>• Written procedures that are well defined.</li> <li>• Role of the Quality Unit or independent quality personnel</li> <li>• Equipment that is appropriately controlled for its intended use</li> <li>• System for appropriate sampling, inspection, and testing of components, intermediates, and <u>product</u></li> <li>• 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> <p>Subsequent sections describe requirements for these key elements in more detail.”</p>

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5	Section V. B. Quality Control Function/224-251	<p>SP believes that the term QC in Section V. B titled “Quality Control Function” requires clarification and differentiation to be more consistent with current thinking and other related guidances (e.g., ICH Q7A) between <del>ov</del> <b>Deleted: e.g.</b> Control (sampling, inspection and testing), and <u>drug product</u> disposition, especially for instituti <b>Deleted: ,</b> with commercial production. We also believe that we can strengthen the Agency’s intent by b <b>Deleted: product</b> responsibility for quality to the front of the section. SP therefore offers the following alternative <b>Deleted: product</b> wording for Section V. B. for the Agency’s consideration:</p> <p>“Quality is the responsibility of all personnel involved in the manufacturing, packaging, testin <b>Deleted: product</b> <u>drug products</u>. Nevertheless, we recommend that final responsibility for quality assurance oversight and approval or rejection <b>Deleted: product</b> of each batch of <u>drug product</u> for use in clinical trials should be assigned to a designated indiv <b>Deleted: product</b> 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>We recommend that every producer establish written procedures defining the responsibilities of an independent Quality Unit or quality personnel. The procedures should describe the responsibilities for personnel in Quality roles as well as other personnel involved in the manufacture and testing of investigational drug products. Key responsibilities to address are as follows:</p> <ul style="list-style-type: none"> <li>• Responsibility for the establishment, review and approval of acceptance criteria that are appropriate with regards to patient safety and extent of knowledge about the <u>drug product</u>, for the various compon <b>Deleted: product</b> <u>drug product</u> (starting materials, primary packaging materials, labeling), intermediates and for the bulk and packaged <u>drug product</u></li> <li>• Responsibility for the establishment, review and approval of <u>drug production</u> procedur <b>Deleted: product</b></li> <li>• Responsibility for sampling, inspection, and testing of components, intermediates, and <b>Deleted: product</b> are frequently defined as “Quality Control.” <b>Deleted: ”.</b></li> <li>• 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> </ul>

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Page	Section/Line	Response
5	Section V. B. (Cont'd) Quality Control Function/224-251	<ul style="list-style-type: none"> <li>Responsibility for appropriate investigation as well as ensuring any necessary corrective actions are taken if unexpected results or errors <u>that</u> occur during production, <u>or</u> testing, or in response to complaints. Deleted: that Deleted: ,</li> </ul> <p>In order to avoid potential contamination of investigational <u>drug product</u> with laboratory reagents, all laboratory 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 of segregation within the room." Deleted: product</p>
6	V. Recommendations for Complying with the Statute/205	<p>The draft guidance recommends "A formal evaluation of the production environment to identify potential hazards" The Agency should explain the intent 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>The bullet point should be revised to read: "The production environment should minimize potential contamination of <u>drug product</u> quality and safety." Deleted: product Deleted: "</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 <u>drug product</u> and <u>the</u> 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 <u>drug product</u> and manufacturing process? We do not intend to recommend the creation of a formal risk assessment document for each <u>drug product</u> and manufacturing process. We do not intend to recommend the creation of a formal risk assessment document for each <u>drug product</u> and manufacturing process. We do not intend to recommend the creation of a formal risk assessment document for each <u>drug product</u> and manufacturing process. Deleted: product Deleted: product Deleted: product Deleted: ". Deleted: ".</p>
6	A. Personnel/220	<p>As indicated in the overall comments regarding clarifying the term "QC" and how that applies here as well especially to those job functions requiring a thorough knowledge of quality principles and systems. We recommend replacing the term "QC" with "Quality." Deleted: "</p>

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Page	Section/Line	Response
7	V. D. Control of Components/280	It appears that the requirement in this section relates to traceability of components from receipt through use in finished drug product batches. We recommend the Agency consider removing the requirements around the need for a log book including specifying what is required. It would be more appropriate to just provide guidance on need for having appropriate traceability of components from receipt through use in finished drug product batches.
8	V.D. Control of Components/296-298	Identity testing should be performed on API received from outside the company, however, identity testing should not be required for intra-company shipments.  Suggested rewording: "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." <i>Deleted:</i>
8	V.F. Laboratory controls/322-325	The term reproducible has a specific connotation in ICH Q2A/B for commercial <u>drug product</u> registration 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:  "We recommend that testing be performed following written procedures which define the methodology and testing <u>parameters</u> and which require documentation of equipment used and results obtained. Analytical information to support batch release (e.g., testing of components, in-process material, packaging) should be scientifically sound and suitable for the specified purpose (e.g., specific, sensitive, accurate, and precise)." <i>Deleted:</i> product <i>Deleted:</i> parameters <i>Deleted:</i>
9	V. G. Container Closure and Labeling/355	Reword sentence that begins: "We recommend" to read "We recommend that labeling and storage operations be controlled <i>using written procedures</i> to prevent..."
9	V. H. Distribution/358 - 365	Distribution to subjects is a GCP responsibility. This is tracked by clinical trial monitors and not by the developers, manufacturers or controllers of the investigational drug products. Eliminate the requirement that distribution to the subject is a GMP responsibility. This clarification then could raise questions around handling of <u>drug product</u> complaints to further clarify Agency should consider inclusion of control around <u>drug product</u> complaints to further clarify <i>Deleted:</i> product <i>Deleted:</i> product encountered at the investigator sites or from the patient from a GCP perspective link back to GMPs.

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12	VI. Special Production Situations. C. 4. Multiple Batch Producers/498	<p>Recommend deleting the requirement to perform an internal performance review when multiple batches of the same <del>product</del> <u>product</u> are made. Current IND regulations (21CFR312.22) require annual reports be made to the Agency, but a periodic quality review is not a statutory requirement until commercial <del>drug product</del> <u>drug product</u> approval (21CFR201.30.10). It is unlikely that more than several batches of the same investigational <del>drug product</del> <u>drug product</u> will be made in a manufacturing process. Thus, the continuing acceptability of batches is assured by requirements of the batches to meet the specifications acceptance criteria that are deemed necessary at the Phase I stage of development.</p>
15	Glossary	<p>Define Phase 1 study. Phase 1 studies include 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 typically included in Phase 1 studies is generally in the range of twenty to eighty. [FDA website]</p>
17	References	<p>Add reference 5 to exploratory IND studies as mentioned in line 389</p>