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**Novartis Pharmaceuticals Comments on the draft Guidance for Industry
*INDs – Approaches to Complying with cGMP during Phase I***

Dear Sir/Madam:

Novartis Pharmaceuticals is pleased to provide these general comments as well as line by line comments on the draft *Guidance for Industry, INDs – Approaches to Complying with cGMP during Phase I*. These comments were generated by quality assurance professionals in Technical R&D from Novartis development sites in East Hanover, New Jersey and Basle, Switzerland.

This draft FDA document provides an opportunity for valuable guidance on how to apply GMP in a flexible manner for the early stage of product development. We strongly advise that FDA develop further GMP guidance on investigational drugs for phases 2 and 3. During these later phases of development, there is still limited manufacturing experience and knowledge of the product is still evolving. We feel that there should be an incremental application of GMP throughout development and that manufacturing controls should increase with the knowledge of the product and the process. 21 CFR Parts 210 and 211, as written in the Proposed Rule and the draft guidance, applied to phases 2 and 3, would place an unnecessary burden on the pharmaceutical industry.

We feel that the basic elements of a GMP system, i.e. trained personnel, qualified equipment, controls to assure product integrity and avoidance of contamination, traceability of material, appropriate documentation and an independent approval system are required throughout all phases of development.

In addition to the request to provide additional guidance for phase 2 and 3, we have recommendations for this draft Phase 1 guidance.

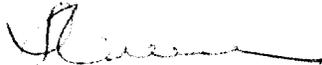
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- Define more clearly to whom the guidance applies. The current draft offers a variety of addressees, e.g., “personsproducing investigational drugs”, sponsors, contractors, commercial manufacturers, academic institutions. We understand that the guidance 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.
- Avoid vague terminology e.g. ‘most’ Phase 1 studies, ‘most’ drugs, or terminology which can be used differently in different contexts, e.g., ‘laboratory’.
- Clarify scope of a Phase 1 study (e.g. purpose of study and type and number of subjects). This can be accomplished by adding a definition.
- The guidance should reflect the FDA thinking about incremental application of GMP in consideration of Phase 2 and 3. GMP expectations should be aligned with FDA’s Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations (September 2004).
- FDA should consider harmonizing this guidance with existing international clinical material guidance e.g. EC Annex 13 and relevant ICH guidelines such as the principles laid down in ICH Q7A applying to APIs and ICH Q9.
- We would not consider the “Screening studies/Microdose Producers” to be listed under the heading “Special Production Situations”, but would propose to incorporate the very useful GMP guidance in this paragraph be added to the relevant sections where the guidance would fit, e.g., facilities and equipment. In contrast, Biotechnological processes and sterile manufacturing ARE indeed specialized **production** situations. In addition, the producers of screening or microdose materials could conclude that this section provides all Phase 1 guidance they would need to consider, which may not be the intention.
- The quality control concept presented in this draft guidance – which appears not in line with the FDAs Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations (September 2004) - needs clarification and should be expanded to define a quality assurance function and quality systems. The term “quality control” itself is used in other guidance as: sampling, testing and inspection, and therefore, may create confusion if not replaced by e.g., quality system.
- Although the same personnel may perform production and testing in smaller operations, we would suggest that separate personnel perform release operations.
- Requiring an “internal performance review” for Biological and Biotechnological Products 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 in order to compare it to previous lots.

We appreciate the opportunity to comment on this draft guidance document that facilitates the production of investigational new drugs while ensuring patient safety. Please contact us if you have questions or if we can be of any further assistance.

Sincerely,



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Technical R&D / Quality Assurance

Docket No. 2005D-0286

**Comments on FDA Draft Guidance for Industry on
Investigational New Drugs**

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Page	Section	Line	Comment
1	I. Introduction	17	Clear definition of the addressee of this guidance is need. The text uses various ways to describe such addressee. Proposal to consistently use 'manufacturers of investigational drugs'.
1	I. Introduction	22	Propose to reword from "...applying quality control (QC) principles" to "...applying quality system principles as outlined below...". Please refer to the comments in line 159 to 171 for further explanation.
1	I. Introduction	31	Clarify what is meant by ' <u>most</u> investigational drugs' or remove the word most.
2	II. Background	55	Reword from "...small- or laboratory-scale production" to "...production of small-scale batches". Avoid the term "laboratory", as it may either refer to the research (non-GMP) laboratory or to an analytical testing laboratory.
2	II. Background	68	The reference in footnote 4 "...additional guidance and or regulations to clarify the Agency's expectations with regard to fulfilling the cGMP requirements when producing investigational drugs for phase 2 and phase 3 clinical studies." should be moved into the body of the text at line 68.
2	II. Background	70-76	It is proposed to delete this paragraph, as the guidance appears to not only provide guidance for "special production situations" or "certain exploratory products", but for the manufacture of Phase I GMP investigational products in general. This is clearly outlined in sections III and V. Otherwise, the guidance may be read and applied in parts only for the "special production situations", negating the rest of the document, which is our understanding, also applies for these situations.
3	II Background	80-81	"Phase 2 and 3 production will continue to be subject to those portions of 210 and 211 that are applicable." This statement does not align with the incremental cGMP approach mentioned earlier in this section (lines 56-58). Furthermore it is not consistent with the plan to develop further guidance for phase 2&3 nor does it reflect the quality system approach to current GMP pharmaceutical regulation. Additionally "The 1991 Guideline on the Preparation of Investigational New Drug Product (Human and Animal) could provide some level of guidance for phase 2 and 3 production until further guidance is available through the Agency."
3	III. Scope	89	Change " investigational product" to " investigational drug product" for clarity.
3	III. Scope	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. Propose to use this definition from FDA website: <u>Phase 1</u> 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

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			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.
4	III. Scope	116-117	<p>We recommend to delete the last part of the sentence: "...and, thus, may want to consider the recommendations described in this guidance."</p> <p>It is understood that this guidance is aimed to investigational <i>drug</i> manufacturers, and that there is different guidance available for investigational APIs via Q7A. We recognize that not all APIs that go into investigational drugs may be covered in the scope of ICH Q7A, but the same QA principles as outlined in Q7A apply for other APIs as well.</p>
4	IV. Statutory and Regulatory Requirements	134	Remove the examples (e.g. those that address expiration dating 211.137(g), and warehousing 211.142). They are not needed and they add confusion. Additionally appropriate warehousing is necessary to assure the integrity of investigational new drugs.
4	IV. Statutory and Regulatory Requirements	136	Clarify what is meant by "most" or delete it.
4	IV. Statutory and Regulatory Requirements	148-150	<p>Suggest the introduction of quality systems in place of quality control procedures.</p> <p>Recommended rewording: "Such actions can also be taken if there is evidence of inadequate quality systems that would compromise the safety of an investigational product."</p>
4-5	V. Recommendations for Complying with the Statute	158-159	Clarify what is meant by "most" or delete it.
5	V. Recommendations for Complying with the Statute	159-171	<p>There appears to be a mixture of the concepts of analytical procedures, quality system procedures, and production procedures in this section. In addition, it is recommended that the agency use terms of a Quality System (see Section V.B.) rather than terms of Quality Control procedures.</p> <p>Recommended rewording: "During product development, the quality and safety 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:</p> <ul style="list-style-type: none"> - Written procedures that are well defined - A system for risk management - Equipment that is qualified (i.e. calibrated and maintained) appropriately for the intended use

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			<ul style="list-style-type: none"> - Accurate and consistently reported data -A system for sampling and testing. -Appropriate level of analytical methods validation (e.g. selectivity, repeatability) -A system for approval or rejection. - Maintenance of the quality and safety of clinical study materials"
5	V. Recommendations for Complying with the Statute	175	<p>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.</p> <p>Recommended rewording: "...to ensure that the investigational drug meets predefined specifications."</p>
5	V. Recommendations for Complying with the Statute	185	<p>Add "...need for additional equipment or qualifying existing equipment <i>for water preparation...</i>".</p> <p>Otherwise, it could be misunderstood to include any kind of equipment.</p>
5	V. Recommendations for Complying with the Statute	194	<p>Reword: "Because the sponsor <i>takes the responsibility</i> for the clinical investigation, we recommend <i>that the sponsor ensures that the producer considers carefully...</i>"</p> <p>The sponsor takes the overall responsibility and ensures that the producer takes his responsibility.</p>
5-6	V. Recommendations for Complying with the Statute	195- 207	<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 rewording: "Use of specialized production facilities and testing laboratories (e.g., contract, academic institutions, clinical research units)</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 quality and safety 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>
6	V. Recommendations for Complying with the Statute	211- 214	<p>The following rewording is suggested to clarify on the intention of the paragraph: "Producers should perform risk assessments for critical parameters of their operations and follow good scientific"</p>

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6	V. A. Personnel	218	<p>Delete the term "...or any combination thereof...", as otherwise, a person could perform a function without training.</p> <p>Recommended rewording:</p> <p>" All personnel should have the education, experience and training to enable that person to perform the assigned function in a GMP environment.</p>
6	V.B. Quality Control Function	224	<p>Change "Quality Control Function" to "Quality System". "Quality Control" is a term that is generally associated with the analytical laboratory. The scope of this section should discuss the entire quality system that should be in place.</p>
6-7	V.B. Quality Control Function	226-251	<p>This section should discuss the quality system (including the establishment of written procedures) that should be established for the manufacture of phase 1 clinical trial materials. We do not recommend the introduction of a new term "QC Plan" to describe this system. We recommend that a discussion for the responsibility for quality be used as an introduction to the section.</p> <p>Recommended rewording:</p> <p>Quality is the responsibility of all personnel involved in the manufacturing, packaging, and testing of investigational drug 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 and analytical testing. 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 prior to batch release review of production records should be carried out by a designated and appropriately qualified individual who is not directly involved with the production or testing of the product.</p> <p>We recommend that every producer establish a written Quality System. For example, a sound Quality System should provide for the following functions:</p> <p>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</p> <p>Establishing, reviewing, and approving production procedures and test procedures</p> <p>Responsibility for sampling, inspection, and testing of components, intermediates, and product. These activities are frequently defined as "Quality Control".</p> <p>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</p>

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			<p>Responsibility for appropriate investigation as well as ensuring any necessary corrective action, in the event that unexpected results or errors occur during production, or in response to complaints.</p> <p>In order to avoid potential contamination of investigational product with laboratory reagents, we recommend that testing activities be separated from production activities.</p>
7	V.C. Facility and Equipment	255-256	<p>Delete the term "laboratory" (see comment on line 55) and clarify what "adequate" work areas and equipment might be based upon.</p> <p>Recommend rewording: "Any facility 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 cross contamination or loss of product quality."</p>
7	V.C. Facility and Equipment	266	<p>We feel that it is important that equipment should be identified, consistent with 21CFR 211 requirements.</p> <p>Recommended rewording: "Equipment used for a particular process should be identified and documented in the production record."</p>
7	V.D. Control of Components	281	<p>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.</p> <p>Recommended rewording: "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. It must be possible to connect the component information to a specific investigational product batch number."</p>
7-8	V.D. Control of Components	286-288	<p>Justification for attributes and acceptance criteria should be documented.</p> <p>Recommended rewording: "However, attributes and acceptance criteria selected for use in the specific investigational drug should be based on documented scientific knowledge and experience."</p>

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8	V.D. Control of Components	296-298	<p>Identity testing should be performed on API received from outside the company, however, identity testing should not be required for intra-company shipments.</p> <p>Recommended rewording:</p> <p>"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>For intra company shipments where unique tamper evident seals are use, confirmatory identity testing is not required.</i>"</p>
8	V.F. Laboratory Controls	322-324	<p>The 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.</p> <p>Recommended rewording:</p> <p>"Analytical tests used in production should be scientifically sound and appropriate for the intended use."</p>
8	V.F. Laboratory Controls	331-332	<p>It is not clear why the IND review is mentioned in this context. This is already stated in III. Scope, and it is questionable that the IND review might bring up unknown acceptance criteria..</p>
9	V.F. Laboratory Controls	340	<p>It is not always possible to allocate twice the amount of sample just for retain because of the small volumes produced.</p> <p>Recommended rewording:</p> <p>"... , we recommend that the sample consist of a quantity adequate to perform additional testing if required later to confirm the identity or integrity of the product..."</p>
9	V. F. Laboratory Controls	342-343	<p>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 actually used in the study. Change the sample retention requirement to also include the option to retain samples for 1 year past expiry of the material (e.g., 5 year expiry plus 1 year = 6 years).</p> <p>Recommended rewording:</p> <p>"We recommend that the samples be appropriately stored and retained for at least 1 year following study termination or 1 year beyond product expiration (e.g., 5 year expiry plus 1 year) with a maximum of 6 years."</p>
9	V. H. Distribution	361-362	<p>Distribution to subjects is a GCP responsibility. This is tracked by clinical trial monitors and not by the developers, manufacturers and controllers of the clinical trial materials. Eliminate the requirement that the distribution to the subjects is a GMP responsibility.</p> <p>Recommended rewording:</p> <p>"As it relates to phase 1 trials, the term "distribution" includes the transport of an investigational product covered by this guidance to clinical investigators."</p>
9	V. I. Recordkeeping	374	<p>Need to specify the records that are produced (e.g. Quality System Reports) or eliminate the bullet.</p>

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10	VI. A. Screening Studies/Microdose Producers	385-413	We suggest to consider using the useful recommendations of lines 398-413 and move it to the relevant sections of the guidance, replacing the term "small-scale laboratories or research" with "small facilities". We feel that this would improve the clarity of the document, and would actually initiate that readers consider the complete guidance document and not only selected chapters which may apply to their situation.
11	VI. B. Multi-Product Facilities	415-430	We suggest to consider using these recommendations move it to the relevant sections of the guidance on facilities, replacing the term "laboratory research" with "small facilities". We feel that this would improve the clarity of the document.
12	VI. C. Biological and Biotechnological Products	498	We recommend that FDA delete the requirement to perform internal performance review when multiple batches of the same investigational product are made. IND regulations require annual reports to be made but a periodic quality review is not required until NDA approval. This type of evaluation is done as part of the development process. However, to require a separate report of analysis of Phase 1 production (where so few batches are produced or reproduced) increases burden to manufacturers without increasing safety of the product to the patient.
	VI.D. Sterile Products/Aseptically Processed Products	511-513	We feel that a recommendations provided in section D are good however they are only listed as recommendations that should be considered. The guidance should stress the importance of maintaining sterile conditions during aseptic processing and sterile manufacturing. Recommended rewording: "Special precautions must be taken for investigational new drugs intended to be sterile. Thorough consideration should be given to controls for aseptic processing. The following examples should be considered."
13	VI.D. Sterile Products/Aseptically Processed Products	518-519	The monitoring of environmental conditions would be important in order to conduct the investigations of sterility test failures. Recommended rewording: "Disinfecting the entire aseptic workstations and monitoring of environmental conditions as appropriate (e.g. before aseptic manipulation, or between different operations)."
13	VI.D. Sterile Products/Aseptically Processed Products	529-530	We have a concern that the proposed guidance does not fully address the sterilization of the investigational product. We therefore recommend inserting the following bullet at line 529: "Where possible, investigational product should be terminally sterilized by heating in an autoclave at 121°C for 15 minutes. Alternative sterilization procedures should be qualified. For products that require aseptic filling, the process (although it may be manual) needs to be qualified by media runs."

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15	Glossary	599	<p>Define Phase I Study</p> <p>Definition from FDA website:</p> <p><u>Phase 1</u> 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]</p>
16	Glossary	600-602	<p>The definition of production should include warehousing. Additionally, there should be a comma separating labeling and laboratory testing in the proposed definition.</p> <p>Recommended rewording:</p> <p>"Production – all operations involved in the preparation of an IND product from receipt of materials through distribution including processing, storage, warehousing, packaging, labeling, laboratory testing and quality control."</p>
16	Glossary	616-618	<p>Include the responsibilities of Quality Assurance unit in the Quality Units definition. Distinguish between QA and QC.</p> <p>Recommendation:</p> <p><u>Quality Control</u> - Checking or testing that specifications are met. [as defined for APIs in Q7A].</p> <p><u>Quality Assurance</u> - 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]</p>
16	Glossary		<p>Recommend the addition of "Quality System" to the glossary.</p> <p><u>Quality System</u> - Business practices that define the organizational structure, processes, and procedures needed to fulfill product/service requirements, regulatory requirements, and achieve customer satisfaction.</p>