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**Novartis Pharmaceuticals Comments on the draft Guidance for Industry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with the knowledge of the product and the process. 21 CFR Parts 210 and 211, as written in the Proposed Rule and the draft guidance, applied to phases 2 and 3, would place an unnecessary burden on the pharmaceutical industry.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.

- Define more clearly to whom the guidance applies. The current draft offers a variety of addressees, e.g., “persons ...producing 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 FDA’s 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,

A handwritten signature in black ink, appearing to read 'Kathleen Greene', with a long horizontal flourish extending to the right.

Kathleen Greene
Executive Director Technical R&D QA US
Novartis Pharmaceuticals