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July 20, 1999

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

**Subject: Response to Draft Guidance for Industry: INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products; Chemistry, Manufacturing and Controls Content and Format, (Federal Register, April 21, 1999, Docket 99D-0674)**

To Whom It May Concern:

Novartis Pharmaceuticals Corporation has reviewed the above-referenced draft guidance. Specific comments, identified by line number, are provided in tabular form in the enclosure.

Novartis believes that this guidance still asks for information which should be provided only at NDA submission, rather than in the IND. Some of the information requested is not available at initiation of Phase 3, and may not be available until the time of NDA submission. We would like the FDA to re-evaluate the use of providing all of the requested information during Phase 3.

Thank you for the opportunity to comment. If you have any questions, please contact Dr. Mathias Hukkelhoven at (973) 781-6035 or Sheryl LeRoy at (973) 781-2735.

Sincerely,

M. Hukkelhoven

Dr. Mathias Hukkelhoven
Executive Director, US Head
Drug Regulatory Affairs

Enclosures: Comments provided in duplicate

99D-0674

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# Novartis' Comments on the Draft Phase 2 and 3 IND Guidance

## General Comments

1. This guidance still requires FULL CMC documentation during Phase 3 of development. Industry may still not know all of this information about the intended commercial product at this time, and some of what is planned may change prior to registration. Novartis believes that the Phase 3 requirements should be reviewed more critically for the value that they give at this stage in development.

2. The stated purpose of the draft Guidance is to assess drug safety and quality of the proposed clinical studies from the CMC perspective. Further, it is stated that information specified in the Phase 3/Pivotal Study section may be submitted via Annual Report if the changes do not affect safety. However, the Guidance does not clearly separate those data to be submitted to meet safety requirements (IND Information Amendments) from the Annual Report requirements.

3. The table format used in the previous draft was easier to follow.

| Lines | Comments |
|---|---|
| 110 & 224 | The guidance should more clearly state that it is not mandatory to follow the pharmacopoeia during the early phases of development (it is implied only). |
| 120-121 | Clarify "a more detailed description of the configuration and chemical structure for complex organic compounds." What specific detail is needed? |
| 133 | Industry should not be forced to disclose the source of starting materials at this phase. A statement indicating that they are commercially available should be adequate. |
| 141 | Remove the phrase "Safety update on reagents, solvents, auxiliary materials" from this sentence. |
| 191 & 282 | Saying that the validation data should be available upon request implies that the Agency expects industry to have completely validated all testing methodology during or prior to phase 2 of development. This should be clarified. |
| 217 | The submission of a stability protocol during phase 2 is premature. Stability studies will be performed, but the need for a protocol seems excessive. |
| 260 | Flow diagrams should not be necessary for simple manufacturing procedures. |
| 285-287 | It appears that CBER requirements are now being applied to CDER requirements for IND documentation. We request a re-evaluation of this. |
| 321 | It appears that the Agency is requesting the same degree of characterization during phase 3 as it would in a typical NDA. Again, we question the use/motive. |
| 358 | Define a *significant* side product. |
| 364 | Indicating the "type of reaction vessel" used is excessive. |
| 401-402 | We question the provision of validation information at this stage. This implies that our validation reports should be done and ready at the start of Phase 3, not for NDA. We request a re-evaluation of this requirement. |

| Lines | Comments, continued |
|---|---|
| 408-409 | The impurity limits should also be set based on toxicological evaluation, not just limited manufacturing experience. |
| 438 | "Each table should contain data from only one storage condition." This is a minor format issue and should not be addressed in this guidance. |
| 466 | Acceptance testing of the drug substance should be discussed in the drug substance section. |
| 510 | Degradation products should be identified and qualified according to ICH guidelines. |
| 522-523 | Listing of suppliers of packaging materials should not be necessary at this stage. Often, they are not relevant to the intended commercial package. |
| 524 | Clarify DMF type. |
| 534 | Photo stability testing should be done during IND phase, but reported in the NDA. |
| 537 | The stability requirements during the IND phase are extensive (like NDA requirements.) |
| 566-567 | What type of "data" should be provided for the placebo to demonstrate the absence of the active ingredient? A statement should suffice. |

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