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Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**Subject: Comments to Draft “Guidance for Industry on Drug Substance:  
Chemistry, Manufacturing, and Controls Information”,  
Federal Register Notice January 7, 2004;  
Docket Number 2003D-0571**

To whom it may concern:

Novartis is a world leader in the research and development of products to protect and improve health and well-being. As a global pharmaceutical corporation, Novartis is supportive of efforts to improve and to harmonize the technical requirements for registration of pharmaceutical products. We appreciate the opportunity to comment on this comprehensive draft guidance in accordance with FDA’s Good Guidance practices.

Novartis is generally in agreement with the goals of the proposed Guidance document, particularly with respect to the following points:

1. harmonization with the Common Technical Document (CTD) format as presented by the International Conference on Harmonization (ICH);
2. cross-referencing to other relevant FDA and ICH Guidance documents

Novartis is concerned about several themes within the draft Guidance that appear inconsistent with the Agency’s recently stated “science-based, risk-based” and “quality by design” initiatives, namely:

1. the increased level of detail and information requested for the CMC section of the NDA/CTD, such as environmental controls for conventional active pharmaceutical ingredient manufacturing processes. Typically, there is little justification that the value added by providing this information is commensurate with the increased burden placed on sponsors and the Agency in collecting and reviewing this information. Indeed, in some cases, the information requested conflicts with current Agency Guidance, such as BACPAC I, intended for regulatory relief;

2. a lack of clarity on how the additional information (if provided to the Agency) would be maintained by the NDA sponsor and the FDA without increasing the burden of post-approval change CMC Supplements for both the sponsor and the Agency

Additional comments are provided in the attached tabular format with line and section number indicated, for ease of FDA use.

These comments are being provided in duplicate in written form and electronically as directed in the Federal Register Notice.

Novartis appreciates the opportunity to submit these comments and looks forward to continuing to work collaboratively with the agency on this important initiative to enhance drug substance chemistry, manufacturing and control initiatives.

Thank you for the opportunity to comment. If you have any questions, please contact Joan A. Materna at 862-778-3379.

Sincerely,

*(signed in original)*

✍ Joan A. Materna

Global Regulatory CMC

**Novartis Comments on:  
Draft FDA Guidance "Drug Substance – CMC Information"  
(Docket No. 2003D-0571)  
December 2003**

| Line Number | Draft Guidance Section | Comment   | Rationale   | Importance<br>1= Major<br>2= Moderate<br>3=Minor |
|-------------|------------------------|---|---|--|
| General     |                        | We appreciate that the guideline is well structured and easy to read.   |   |  |
| General     |                        | It is preferred to separate references to the dossier filing requirements and the GMP requirements  | Mixing reference to dossier filing requirements (in which ICH harmonization has advanced with respect to the CTD) and the GMP requirements under FDA Compliance authority may result in less clarity in the dossiers.   |  |
| General     |                        | The draft gives information on a new guideline (under development) for "fermentation derived drug substances and intermediates and associated drug products". We are looking forward receiving this guideline and are expecting that it will also cover conventional fermentation techniques  |   |  |
| General     |                        | The guidance does not distinguish anymore between NDA and ANDA. Furthermore the referenced guidelines are all related to new drug substances.   | We would like to point out that this is in contradiction to approved guidelines distinguishing between new and existing drug substances (e.g. FDA Guidance for Industry "ANDAs: Impurities in drug substances").  | 2  |
| General     |                        | Throughout the document the definitions "process step", "manufacturing step", manufacturing operation", "reaction steps" are used. Only one definition should be used or otherwise the different definitions should be explained in the glossary  | Using various terms for the same item is confusing and should in the interest of clarity be avoided   | 1  |
| General     |                        | There are several paragraphs dealing with bovine-derived materials and restrictions which have to be applied. We feel that a general prohibition of any raw material derived from a BSE-country according to 9 CFR 94.11 cannot be the intention of this guidance. Refer also to footnote on page 57 where is indicated "unless otherwise exempted by the Agency". We think there is a need for clarification for which bovine-derived products exemptions are applicable and which ones are regulated by this guideline. | A risk based approach (organs used, age of animals, feed stuff used, slaughterhouse precautions etc) rather than a geographical approach (except for the exclusion of high-risk countries like UK and Portugal) would be beneficial. Otherwise, one single infected animal in a previously BSE-free country would automatically disqualify any bovine material from this country from the use in pharmaceuticals. Is this the true intention of the statements? | 1  |

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| 109-110     | II.A.                  | Duplicate information should not be required in the DMF and NDA. Please clarify.  | Duplicate information should be limited because it would potentially be reviewed twice which is unnecessary work. Also, there would also be unnecessary work by the NDA holder.  | 2  |
| 200         | II.D.1                 | footnote 9: If a firm has DS information filed in an NDA and sells the material to a second firm, does the firm really need to duplicate filing the same information in a DMF? Please clarify.  | This is again duplicate effort. Why is the recommendation different at CVM?  | 2  |
| 236         | II.D.2                 | Some of this DMF information could be unavailable to the firm.  | Duplicate information should be limited to avoid unnecessary work. Some information may be proprietary, therefore would not be available.  | 2  |
| 378         | IV.A. (S.2.1)          | Please clarify if testing laboratories mean both release and stability.   | For clarification.   | 2  |
| 383-384     | IV.A. (S.2.1)          | Please clarify what is meant by multifacility? Please clarify why building numbers are necessary to provide?  | Such information was previously described in Type I DMFs. According to Federal Register/Vol. 65, No. 8/ January 12, 2000: "Final rule to 21 CFR Part 314: Elimination of DMFs Type I" such information should be available on site only. | 1  |
| 385         | IV.A. (S.2.1)          | The exact room need not be identified.  | Too detailed.  | 2  |
| 387         | IV.A. (S.2.1)          | Please clarify what is meant by a "US Agent". Does the USA agent have to be a person in the USA? Shouldn't this information be in the 356h, if necessary at all for NDA holders?  | Agents are typically designated for DMFs .   | 2  |
| 391         | IV.A. (S.2.1)          | Does the contact person need to be someone in the USA or at the foreign facility? Shouldn't this be on the 356h?  | For clarification.   | 2  |
| 410         | IV.B. (S.2.2)          | Consider saying "final drug substance" rather than "drug substance release testing".  | It is not helpful to include release testing in the flow diagram. This information is available elsewhere in S.2.1.  | 1  |
| 414         | IV.B.1 (S.2.2)         | Critical within what you have validated?? Critical for quality issues?? The way it is defined now it is either all or nothing. Give example of critical for clarification.  | There should be very few instances where a step is 'critical'.   | 3  |
| 406-435     | IV.B.1 (S.2.2)         | How do you fit all this information in the flow diagram? E.g. auxiliary materials are not synthesis relevant and should not be included. Likewise, the operating parameters can be seen in the textual description of the manufacturing process | To include all of the requested information in the flow diagram will almost negate the purpose of the Manufacturing directions.  | 2  |
| 427         | IV.B.1 (S.2.2)         | Please clarify what is intended by operating parameters for each step? Are these binding and cannot be changed without PAS?   | For clarification.   | 2  |

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| 441         | IV.B.2<br>(S.2.2)      | Delete requirement for reporting the scale except for the conversion of the final intermediate to the final drug substance.  | BACPAC I states that scale changes do not need to be reported up to the final intermediate, therefore it is unnecessary to specify scale in the original application; just specify ratios.   | 2  |
| 443         | IV.B.2<br>(S.2.2)      | Change <b>all</b> to <b>quality relevant</b> process controls  | Only process controls that have an influence on quality are relevant   | 1  |
| 454         | IV.B.2<br>(S.2.2)      | Delete requirement to specify equipment used up to the final intermediate.   | BACPAC I states that equipment does not need to be reported up to the final intermediate.  | 2  |
| 471         | IV.B.2<br>(S.2.2)      | Delete the phrase, "identification of processes that involve combining intermediate or drug substance batches" from the information needed for the manufacturing directions .  | This is GMP.   | 2  |
| 488-491     | IV.B.2<br>(S.2.2)      | <i>A statement should be provided that bovine-derived materials from bovine spongiform encephalopathy (BSE) countries as defined by the U.S. Dept. of agriculture (9 CFR 94.11) are not used or manipulated in the same facility.</i> The list of countries referred to in 9 CFR 94.11 would exclude almost all European countries as source countries for bovine-derived materials. We understand this position for live animals, meat or foodstuff derived directly therefrom. We do not agree for raw materials used in fermentation processes or semisynthetic drug substance processes. We propose to modify this sentence in the sense that <b>high-infectivity tissues may not be used or manipulated in the same facility.</b> | In fermentation processes often milk or milk derived products like skim milk, lactose, caseins are used. These raw materials are simultaneously used as food (even baby food) without additional restrictions. It is clear that the basics for risk minimization have to be kept i.e. the milk has to be sourced from healthy animals being fit for human consumption. Raw materials for semisynthetic processes have normally undergone rigorous manufacturing steps prior to conversion to raw materials. Typical examples are gelatin and tallow derivatives like stearates. Acceptable conditions are clearly defined in corresponding EU and FDA guidelines (EMA/410/01 Rev. 2 or Guidance for Industry "The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by BSE in FDA-Regulated Products for Human Use") | 1  |
| 491         | IV.B.2<br>(S.2.2)      | Define what is needed for a multiuse facility and what is multiuse?  | For clarification.   | 2  |
| 509         | IV.B.2<br>(S.2.2)      | Too much detail is required for operating parameters.  | Too restrictive. How are changes to operating parameters then implemented?   | 3  |
| 510         | IV.B.2<br>(S.2.2)      | Environmental controls should not be required for regular standard chemistry.  | Too restrictive. How are changes to environmental controls then implemented?   | 3  |
| 522         | IV.B.2<br>(S.2.2)      | Delete "critical or otherwise" form the statement that All process controls, critical or otherwise, should be included in the description of the manufacturing process.  | Only process controls that have an influence on quality are relevant   | 1  |
| 542         | IV.B.2<br>(S.2.2)      | Delete '...and unfinished drug substance'  | This would mean double testing   | 1  |

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| 552         | IV.B.3<br>(S.2.2)      | Exchange: 'described' with 'mentioned'   | Reprocessing is repeating of a step. Since the description is already given no further description is needed. (See 3.a.)  | 2  |
| 561         | IV.B.3<br>(S.2.2)      | Please clarify what is meant by 'when warranted' when referring to the submission of validation data for critical                                  | Process validation information for drug substances is not provided to the NDA.  | 2  |
| 581-589     | IV.B.3a<br>(S.2.2)     | Delete entire paragraph.   | Reprocessing is only done to improve the quality, not to decrease it. The next paragraph (591-598) covers the necessary information.  | 2  |
| 605-609     | IV.B.3b<br>(S.2.2)     | Delete <i>..repetition of multiple reactions steps is considered to be reworking</i>   | Is in contradiction to ICH Q7A where reworking is defined as " <i>subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process.....</i> " | 1  |
| 607-609     | IV.B.3b<br>(S.2.2)     | Delete sentence.   | Only material complying with testing at each step would be used. Thus, no unexpected impurities are likely to occur.  | 1  |
| 669         | IV.C                   | Delete "auxiliary materials".  | See comments for Lines 406-435  | 2  |
| 688         | IV.C.1<br>(S.2.3)      | <i>In general, starting material and API starting material will not be identical</i> . Reference to the "API Starting Material" should be omitted. | The API starting material is seen as a synonym for the formerly used term 'critical intermediate' where full GMP started including process validation. This is not relevant for the dossier submission.   |  |
| 713         | IV.C.1<br>(S.2.3)      | Please clarify what is meant by flow diagram under the section of starting material.   | A flow diagram of the SM itself is not registration relevant and should not be required.  | 1  |
| 725-727     | IV.C.2<br>(S.2.3)      | <i>When contamination with viral adventitious agents or TSE agents is a concern, additional information may be warranted....</i>                   | This is acceptable as long as the same principles apply as above mentioned (comment to lines 488-491).  | 1  |
| 736         | IV.D. (S.2.4)          | Specifications and test methods for auxiliary materials are not relevant and should not be given   | Auxiliary materials do not have a negative influence on the quality of the substance like solvents could through by-products  | 2  |
| 772-777     | IV.D. (S.2.4)          | Delete this section  | Only critical tests are relevant and should be mentioned at all. There is no positive effect on quality.  | 1  |
| 775         | IV.D. (S.2.4)          | What is the advantage of separating out the critical tests? Will there be different regulatory requirements for critical tests?                    | There should be very few instances where a step is 'critical'.  | 3  |
| 780-781     | IV.D. (S.2.4)          | Delete the requirement for the submission of experimental data to justify critical process controls.   | Process validation information is not provided to the NDA.  | 2  |
| 800         | IV.D. (S.2.4)          | Please clarify why a DS specification is necessary at all if a test is performed on the intermediate satisfying the need?                          | For clarification.  | 2  |

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| 810             | IV.D. (S.2.4)          | We suggest that results need not be provided on the DS COA if the test was not run on the drug substance itself.   | This is redundant.   | 2  |
| 952-954         | V.A.2 (S.3)            | Delete sentence  | It is not appropriate to repeat information already given in   | 2  |
| 992-995         | V.A.2 (S.3)            | Please provide an example of when a Bioavailability study would be required to conclude whether the physical properties of the DS will have an impact.                         | For clarification.   | 2  |
| 1057-1060       | V.B.2 (S.3.2)          | Delete the need to provide structural characterization data for impurities and the summary of the route of synthesis for impurities if they were independently prepared.       | Too much information for the NDA. Not necessary. Structural congruency should be demonstrated and suffice.   | 1  |
| 1083, 1111-1114 | VI.A (S.4.1)           | Delete mentioning of drug product  | Documents are for drug substance – drug substance may be used for different drug products. Expenditure not justified   | 1  |
| 1108-1110       | VI.A (S.4.1)           | Please clarify when an analytical procedure would only be used for stability and not release? Why would the tests be kept in different places in the event there are examples. | For clarification.   | 2  |
| 1126            | VI.A (S.4.1)           | Please provide an example of where the shelf-life criteria would be indicated on the Specification?  | For clarification.   | 2  |
| 1143            | VI.A (S.4.1)           | Please provide examples of potential PQIT tests  | For clarification.   | 2  |
| 1149-1150       | VI.A (S.4.1)           | ....."designation of certain tests such as for description, identification, assay, or impurities as PQIT would not be considered appropriate.                                  | The description of PQIT is not in line with USP General Notices (Procedures, p. 7 USP 27):... <i>Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all of the requirements in the monograph defining it. However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial standards before the batch is released for distribution.</i> Furthermore ICH Q7A allows "...the impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data ....." which is in line with USP. Non-batch wise testing of by-/degradation products may be done under certain circumstances such as: validated process, batch consistency data demonstrating consistent quality of the product. Provided that all prerequisites for a PQIT as mentioned in the draft guidance are fulfilled we would | 2  |

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|             |                        |  | as suitable for PQIT as long as sufficient sets of data show clear evidence for a correlation between tests performed on a batch to batch basis (e.g. assay, absorbance, specific optical rotation..) and the level of impurities. In case of any out-of-expectation or out-of-specification event, impurities would have also to be tested during analysis of such batches |  |
| 1189        | VI.A (S.4.1)           | <i>Additional guidance....</i> Please include guidance "ANDAs: Impurities for Drug Substances" and others as applicable.   | Only guidances for new drug substances are mentioned. According to line 28 "Introduction" this guidance is also for ANDAs.  | 2  |
| 1242        | VI.C (S.4.4)           | Delete non clinical studies; i.e. pharmacology (batches) from the requirement to provide batch analysis results.   | Batch analyses are only necessary for toxicology batches, not pharmacology batches.   | 2  |
| 1267        | VI.C.1 (S.4.4)         | Please clarify that the summary of analytical changes should only be provided for significant changes, i.e. change from paddle to basket in running dissolution. | For clarification.  | 2  |
| 1414-1417   | VIII (S.6)             | Delete the requirements to provide the suitability of the container closure system.  | The stability data supports the re-test period, therefore the suitability of the container closure system is therefore demonstrated in the application.   | 2  |
| 1436        | IX.B (S.7.2)           | What is the advantage of filing a post approval stability protocol?  | The protocol should be optional. Full ICH stability is generally performed to qualify DS changes. The protocol does not reduce this requirement.  | 2  |

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| 1449        | IX.C.1<br>(S.7.3)      | Please add the comment that primary stability needs to be done on the final synthesis as per line 905.   | For clarification.  | 2  |
| 1526-1528   | X.A (A.1)              | <i>If bovine-derived material from BSE countries as defined.... are used or manipulated in the same facility, additional information should be provided, such as whether dedicated equipment is used</i> | The use of dedicated equipment for use or manipulation of bovine-derived materials is too stringent. For rationale and proposal see comment to lines 488-491  | 1  |
| 1565-1569   | X.B (A.2)              | <i>For synthetic or semisynthetic drug substances reduced testing of materials or .... Validation of removal and/or inactivation or adventitious agents can be appropriate.....</i>                      | Please specify to provide an unambiguous interpretation of this paragraph   | 2  |
| 1588-1590   | X.B (A.2)              | <i>Certifications and/or certificates relating to the use of bovine-derived materials and sourcing of materials from BSE countries ....</i>  | Which kind of certificates are meant ? Are this company confirmations, certificates from suppliers or certificates from an official authority ? Please specify.   | 2  |
| 1606-1609   | X.B (A.2)              | <i>...results to confirm, ... ,that the product is free from viral contamination should be provided. ...results for viral testing of unprocessed bulk should be provided.</i>                            | A vast majority of substances used as nutrients for conventional fermentation are well established in pharmaceutical and, in part, but more profoundly, alimentary use. Experience over decades have not revealed any impairment of patient/consumer safety associated with virus contamination. Indeed, we are not aware of any reported adverse event that could be linked to virus transmission of any of the above-mentioned substances. Therefore it is felt an unnecessary burden on pharmaceutical manufacturers and regulators having to assess virus safety for, e.g., milk-derived substances. Most manufacturing processes of DS combine manufacturing and purification conditions which kill or at least inactivate viruses. E.g. classical fermentation products or semi-synthetics derived thereof, normally combine high temperature treatments, with organic solvent extractions and washings, column steps, crystallizations and filtrations which make it very unlikely that viruses will be carried over in an activated state. Moreover human-disease causing viruses normally do not replicate in bacterial cultures used in classical fermentation products. This should be considered for the final guideline in order to avoid unnecessary burden of the pharmaceutical industry. | 2  |

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| 1677        | Attach I               | Reference to ICHQ7A should be avoided.  | Guidance for GMP and guidance for dossier requirements should be strictly separated as it confuses the reader.  | 1  |
| 1690-1691   | Attach I               | Reconsider the entire concept of "significant non-pharmaceutical use".  | We acknowledge that it can be viewed as important that the chemical should be commercially available. However, we strongly disagree that it should have a significant <b>non-pharmaceutical</b> use. We do not see any value added in this requirement.   | 1  |
| 1699        | Attach I               | <i>...only a small fraction...</i>  | This term is completely open for interpretation and of no help.   | 1  |
| 1701-1705   | Attach I               | Delete: <i>if the quality of the chemical made for the non-pharmaceutical market is insufficient.....the purification operations should be described....</i>  | We see no value added in having to describe the purification process. The adequate quality of the starting material is guaranteed by its specifications.  | 1  |
| 1743        | Attach I: I.A          | Give minimum of reaction steps  | For clarification.  | 2  |
| 1784-1790   | Attach I: I.C          | Modify: <i>...of selecting proposed starting materials, a significant level is considered to be greater than 0.10 percent in the drug substance.....</i>  | The definition and use of a material as starting material should not be forbidden based on the fact that it is a source of impurities as long as these impurities are qualified in accordance to the relevant guidelines. Impurities above 0.1 percent have to be qualified in any case and therefore such requirement seems to be irrelevant. For generic drug substances reference should be made to guidance "ANDAs: Impurities in Drug Substances" and the respective "Impurities decision trees". For new drug substances reference should be made to ICH Q3A (R) "Impurities testing: impurities in new drug substances" and the respective "decision tree for identification and qualification". | 1  |
| 1792-1797   | Attach I: I.C          | <i>... a starting material should be at or before the point in the manufacturing process where TSE agents can be introduced in the process.....</i> The wording of the paragraph should be changed to clarify the meaning of a starting material. | This requirement can hardly be fulfilled for purchased starting materials (e.g. lactose or tallow derivatives) which becomes a starting material in our process. Of course the requirement applies for enzymes which are introduced during the process steps performed in our facility.   | 1  |
| 1815-1818   | Attach I: I.D          | <i>If advanced techniques....are needed....the chemical is not an appropriate candidate for Designation as starting material.</i> We disagree with this statement.  | If such methodology is used to <b>control</b> the quality of the chemical then this chemical can very well be a candidate for starting material   | 2  |

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| 1835        | Attach I: II           | Delete: <i>..regardless of whether these chemicals are being proposed as starting materials.</i>   | If compounds with a <b>insignificant</b> non-pharmaceutical market can, under certain circumstances, be proposed as starting materials (as suggested by the guidance), it does not make sense to request the flow diagram of their synthesis. Would the information provided in such a flow diagram be binding for the steps leading up to the starting material without significant nonpharmaceutical?? If so, then the term <b>starting material is misleading for such a chemical</b> | 1  |
| 1863-1867   | Attach I:II.C          | Please re-phrase: <i>...there can be a greater potential for carryover (1) when the proposed starting material is the first isolated and purified chemical (counting backwards from the drugs substance) consistent with the selection principle concerned with the carryover of impurities or (2) based on the proximity of the starting materials to the drug substance...</i> | Wording is extremely difficult to understand.  | 1  |
| 1883        | Attach I:II.D          | Delete the statement <i>"A description of the uses other than for drug substance production"</i>   | It is of no added value for the submission and extremely time-consuming for industry to obtain   | 1  |
| 1884        | Attach I: II.D1        | <i>"both drug substance production and other markets"</i> should be dropped.   | What if a chemicals manufacturer specializes in supplying purified material for drug substance production but leaves the supply of the other markets with less pure product to other manufacturers??   |  |