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Date June 22, 2004
Your letter -
Your initial -

Docket No. 2003D-0571
Comments on the Draft Guidance for Industry
"Drug Substance: Chemistry, Manufacturing, and Controls Information"

Dear Sirs,

Please find enclosed our written comments on the above mentioned Docket No. 2003D-0571 regarding the draft guidance for industry entitled "Drug Substance: Chemistry, Manufacturing, and Controls Information".

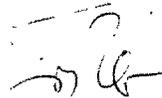
Should you have any questions, please feel free to contact us at any time.

Best regards,

Sandoz GmbH



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2003D-0571

C9

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**Comment to FDA Guidance for Industry
 “Drug Substance – Chemistry, Manufacturing, and Controls Information” (Draft January 2004)**

General Comments
We appreciate that the guideline is well structured and easy to read.
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”).
Throughout the document the definitions “process step”, “manufacturing step”, “manufacturing operation” are used. Only one definition should be used or otherwise the different definitions should be explained in the glossary
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
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 can not 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 irrespective of the geographical origin or excluding only the high risk countries like UK and Portugal and which one are regulated by this guideline.

Reference Line for item	Specific Item	Comments
383-384	Building numbers for multi facilities campuses....	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.
473 431	...yield ranges for each manufacturing step ...expected yield for each reaction step	Please clarify whether the meaning of “manufacturing step” is the same as “reaction step”. If YES, we propose to harmonize the wording in the document.

Comment of Sandoz GmbH, A-6250 Kundl, Austria prepared by Birgit Laussamayer, 03 May 2004
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488 - 491	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.	<p>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.</p> <p>Rationale: 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.</p> <p>Raw materials for semisynthetic processes have normally undergone rigorous manufacturing steps prior conversion to raw materials. Typical examples are gelatin and tallow derivatives like stearates. Acceptable conditions are clearly defined in corresponding EU and FDA guidelines (EMEA/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")</p> <p>Proposal: We propose to modify this sentence in the sense that high-infectivity tissues may not be used or manipulated in the same facility.</p>
605-609	..repetition of multiple reactions steps is considered to be reworking....	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> ”

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725-727	When contamination with viral adventitious agents or TSE agents is a concern, additional information may be warranted....	This is acceptable as long as the same principles apply as above mentioned (comment to lines 488-491).
1135-1188 1149-1150	Periodic Quality Indicator Tests ”designation of certain tests such as for description, identification, assay, or impurities as PQIT would not be considered appropriate.	<p>The description of the PQIT is not in line with USP General Notices (refer to Procedures on p. 7 of 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></p> <p>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.</p> <p>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.</p> <p>Provided that all prerequisites for a PQIT as mentioned in the draft guidance are fulfilled we would consider impurities testing 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.</p>
1189	Additional guidance....	Only guidances for <u>new</u> drug substances are provided

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1526-1528	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	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
1565-1569	For synthetic or semisynthetic drug substances reduced testing of materials or Validation of removal and/or inactivation or adventitious agents can be appropriate.....	Please specify to provide an unambiguous interpretation of this paragraph.
1588-1590	Certifications and/or certificates relating to the use of bovine-derived materials and sourcing of materials from BSE countries....	Which kind of certificates are meant ? Are this company confirmations, certificates from suppliers or certificates from an official authority ? Please specify.

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1592-1616	Chapter on Viral adventitious agents	
1606-1609	<p>...results to confirm, ... ,that the product is free from viral contamination should be provided. ...results for viral testing of unprocessed bulk should be provided.</p>	<p>Please be aware, that a vast majority of substances used e.g. 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.</p> <p>Most manufacturing processes of actives combine manufacturing and purification conditions which kill or at least inactivate viruses. For instance 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.</p>

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<p>1683-1685</p>	<p>A drug substance that is used to synthesize another drug substance is not an appropriate candidate for designation as a starting material</p>	<p>This requirement is more restrictive than the corresponding ICH Q7A requirement, which asks for “...is incorporated as a significant structural fragment into the structure of the API. ... API starting materials are normally of defined chemical properties and structure” <i>Example:</i> 6-APA (6-aminopenicillanic acid) is an intermediate substance manufactured from the drug substance Penicillin V Potassium. In further reaction steps 6-APA can result in another drug substance Amoxicillin Trihydrate: Penicillin V Potassium (DS) → 6-APA (intermediate) → several reaction steps → Amoxicillin Trihydrate (DS) → Amoxicillin Sodium (DS)</p> <p>As a drug substance (DS) is clearly characterized and controlled by a specification there is no reason why a DS should not be considered to be a starting material for another DS-process. The previous guideline (1987) did not include this request, and no reason can be seen to change this aspect.</p>
<p>1742-1746 1753-1757</p>	<p>A chemical proposed as starting material should be separated from the final intermediate by several reaction steps that result in isolated and purified intermediates..</p> <p>A reaction followed by multiple purifications should be counted as a single reaction step..... an interconversion of a salt to or from its free acid or base form should not be counted as a reaction step for the purpose of evaluating propinquity...</p>	<p>This requirement is more restrictive than the corresponding ICH Q7A requirement, which asks for “...is incorporated as a significant structural fragment into the structure of the API. ... API starting materials are normally of defined chemical properties and structure”</p> <p>No reason can be seen why there should be several reaction steps between the starting material and the final intermediate. Even one reaction step plus multiple purification steps can result in an isolated and pure final intermediate.</p> <p>“<i>Several</i> reaction steps” will lead to different interpretations within authority and within industry.</p>

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1784-1790	...of selecting proposed starting materials, a significant level is considered to be greater than 0.10 percent in the drug substance.....	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 FDA Guidance for Industry “ANDAs: Impurities in Drug substances” and the respective “Impurities decision trees”. For new drug substances reference should be made to ICH Q3A (R) “Note for guidance on impurities testing: impurities in new drug substances” and the respective “decision tree for identification and qualification”.
1792-1797	... a starting material should be at or before the point in the manufacturing process where TSE agents can be introduced in the process.....	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. Proposal: The wording of the paragraph should be changed to clarify the meaning of a starting material.
1863-1867	...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 drug 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...	Wording is extremely difficult to understand.....please transform