

DSM Anti-Infectives B.V.



A. Fleminglaan 1, 2613 AX Delft
P.O. Box 425, 2600 AK Delft, The Netherlands
Telephone 0031 (0) 15 2799111

1100 0 0140 000

Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
USA

Your reference

Our reference
CO/MK/02

Direct line
+31-15-279 2361

Delft
2004, 1 April

Docket No. 2003D-0571

Dear Sir or Madam,

Please find hereunder our comments on FDA's Draft "Guidance for Industry: Drug Substance, Chemistry, Manufacturing and Controls Information" (January 2004).

Sincerely yours,

Chris Oldenhof, Ph.D.
Senior International Regulatory Adviser
DSM Anti-Infectives B.V.
PO Box 425 (mailstop 530-0373)
2600 AK Delft
The Netherlands
Fax: + 31 15 279 3632
Email: chris.oldenhof@dsm.com

C.C.
Dr. Moheb Nasr (HFD-800)
Dr. Steve Miller (HFD-530)

2003D-0571

C1

DSM Anti-Infectives, a Business Group of the Dutch company DSM, is one of the world's leading manufacturers of antibiotic APIs and –intermediates. Our Business Group has ten wholly- and partly owned manufacturing sites worldwide, and is the holder of about twenty US DMFs (many of which were formerly approved AADAs for bulk) submitted to and in majority previously reviewed and found acceptable by the FDA. We highly appreciate this opportunity for submitting our comments on the above-mentioned Draft Guidance that contains requirements that are of direct relevance and in fact of great importance to our products.

Our comments hereunder have been categorized into “General Comments” and “Specific Comments”. The comments that are in our view of the highest importance have been highlighted by bold text.

GENERAL COMMENTS AND CONSIDERATIONS

- **We commend the FDA for the high degree of clarity, the science-based approach and the thoroughness that characterize this Draft Guidance. There are, however, also important exceptions to this, such as the following two examples:**
Firstly there is now a requirement in section 2.2 that full process details, quantities, times and temperatures are given for *all* processing steps rather than focusing on critical process steps. This goes against a risk based approach and the principles of looking at critical steps in ICH Q7a. Our proposal is therefore to restrict such requirement to critical, final steps. Secondly, possibly inadvertently, it introduces a requirement to include environmental controls for the production facilities as part of the process description. See figure 1. This is, however, covered by cGMP (ICH Q7a) and should not be a regulatory requirement unless sterile drug substances are being manufactured.
- **DSM Anti-Infectives is a dedicated manufacturer of APIs. The industry sector of dedicated API manufacturers is suffering heavily under extremely strong regulatory restrictions on its possibilities to implement continuous improvement and innovation. Especially in multi-customer supply situations for APIs these restrictions even form an insurmountable barrier to progress. These restrictions are therefore threatening the continuity of the companies within our sector that are in full regulatory compliance. Because of this important flaw in the regulatory post-approval change authorization systems, the content of the draft guidance results in ambivalent feelings for us, because it would imply a further increase in the amount of detail to be submitted on the drug substance CMC. The more detail is included in API regulatory submissions (DMFs), the higher the regulatory restrictions on change / improvement thereafter. We know that the FDA is well aware of these serious problems for DMF holders in multi-customer supply systems and we once more express our hope and urgent need for an adequate solution to be implemented the soonest. We also are very much aware that within the 21st Century GMP Initiative the FDA aims for the development of a regulatory environment that will foster innovation and continuous improvement. Also within this context it will**

therefore be very important to avoid requirements for submitting very detailed information.

In addition, this strong increase in the amount of detail to be included in submissions will overall lead to a probably dramatic increase of the number of Supplements, because even changes in minor details will then affect the content of the approved Application. We believe that this important increase in workload at the FDA would be contrary to FDA's current 21st Century Initiative that, amongst others, aims for an important decrease in the number of to be submitted Supplements.

- Throughout the Draft Guidance reference is made to many different ICH Guidelines. However, the scope of these ICH Guidelines is restricted to new drug substances whereas the Draft Guidance is intended to apply to also older, existing drug substances. This inconsistency should be resolved by either rewriting of the Draft Guidance in such a way that reference to the ICH Guidelines that have a broader scope will be deleted or by revising the scope of the Draft Guidance such that it will be identical to the scope of the ICH Guidelines.

SPECIFIC COMMENTSLines

53: We propose that the words “or starting material” will be inserted after “intermediate”. This will secure the flexibility to choose for this option if there is a sound rationale to do so.

53-54: The term “Conventional fermentation” should be defined in the Glossary. We propose the following definition will be adopted, in accordance with the ICH Q7A Guideline (see especially its Paragraph 18.11):
“The production of APIs of low molecular weight, such as antibiotics, amino acids, vitamins and carbohydrates (as opposed to high molecular weight APIs such as proteins and polypeptides) irrespective of whether production strains are being used that have been selected by either classical mutation or by r-DNA techniques.”
We would like to emphasize that it is important to consistently adhere to the ICH Q7A principle that fermentations as herewith defined are conventional ones, also when rDNA derived production strains are being used.

67: In line with our comment on lines 53-54, the words between brackets should be changed into: “either or not using r-DNA technology”.

111: Delete “the” in “...will be the provided...”

213: The established procedures are that the DMF holder submits the original LOA in duplicate to the FDA and forwards a copy of the LOA to the applicant. Therefore, the wording should be changed from “...to the applicant and the...” to: “...to the FDA and a copy...”:

274: “used” should be “uses” (typo)

421-422: The term “structurally complex reagents” should be defined in the Glossary. An undefined term such as this one will cause widely diverging interpretations.

427: We propose to delete this sentence. The operating parameters will already be included in the process description and may be too “bulky” to fit into the flow diagram.

443 and

449 onwards: This requires full details for the description of each process step - all quantities, manufacturing scale, process parameters and all process controls. This is much more restrictive as compared with other existing FDA guidance. This would not be in line with a risk-based approach that should focus on more detail for critical and final processing steps. See also our general comment on this above.

- 475-484:** We request that the option will be available to define the substance produced by fermentation as the starting material for a semi-synthetic API, for cases when there will be a sound rational to do so.
- 459: To better reflect current FDA thinking we recommend stating here: "(e.g. HPLC or PAT)"
- 510 It should not be required to submit details of environmental controls of facilities unless sterile drug substances are involved. For non-steriles this is adequately covered by cGMP.
- 512-514 & 521-522** The requirement to register all process controls is far too restrictive (see our comments above).
- 538 Omit "environmental conditions" (see above)
- 546 Omit boxes referring to environmental conditions (see above)
- 613 Reworking at an early process step to give equivalent quality of an intermediate is not prior-approval according to BACPAC I. We propose that the wording will be brought in line with BACPAC I.
- 643, 647-649:** A requirement to describe recovery of solvents and regeneration of column materials, catalysts etc., including also process controls is far more restrictive than what has been common practice thus far. It is another example of a sharp increase in the required detail of to be submitted information, and contrary to new, emerging FDA policies (see also our above General Comment on this). We believe that appropriate specifications should suffice for these materials.
- 658-662: For the sake of clarity we think it will be useful to specifically mention here that combining tailings of released batches into a new batch is not reworking but reprocessing.
- 698: We recommend that, for the sake of clarity, at the end of this sentence a reference will be made to Attachment 1, where the degree of contribution to the structure of the drug substance is further explained.
- 818 It should not always be required to test for assay for intermediates. It is much more relevant (and often sufficient) to monitor the impurity profile.
- 890-911:** This section does not take into account that for quite old, well established drug substances the original process development information may not be available anymore or may not be (fully) in line with current requirements. It should be stated in this section that in such situations this information will not be required.
- 925-938:** The use of many of the described techniques to confirm the chemical structure should relate to new chemical entities and not to existing APIs. For APIs for which a monograph exists in the USP the compendial identification test method should suffice.

- 965-970: We propose to include that the extent of physicochemical information should also depend on whether the API is a new one or an existing one.
- 1028, 1037 and 1055: The term "significant quantities" should be defined in the Glossary.
- 1082-1084: It would be useful if it would be explained here what the interrelation should be between the specifications of the drug substance manufacturer and the specifications of the applicant.
- 1110: The term "sunset provisions" should be included in the Glossary.
- 1126: After "shelf-life" the words "or retest period" should be inserted: Retest period is the usual requirement for (relatively stable) APIs.
- 1129: In Table 1 in the row on Heavy Metals "0.001%" should be "NMT 0.001%"
- 1129: In Table 1 in the column on "Tests" the term "Unspecified Impurities" is used twice on page 31. This term should be defined in the Glossary.
- 1142-1143: We propose that no discrimination will be made between a drug substance specification and a PQIT. In other words, it should be possible to have PQITs as part of the total set of specifications, provided there will be a sound rationale for these.
- 1149-1150: Testing for heavy metals is a typical example of a test that may often be suitable for a PQIT approach or even for complete deletion. (see also lines 1316-1319 of the Draft Guidance!). However, the reference to "impurities" in a general sense, as is done in line 1149, suggests that PQIT would not be appropriate for heavy metals testing. We suggest therefore that the term impurities will be narrowed down to e.g. "related impurities".
- 1325: The term "sunset test protocol" should be defined in the Glossary.
- 1332-1333: This sentence is quite puzzling. Is it intended to say that the "test to be added" is making another test redundant and that a "sunset test protocol" for the redundant test could be considered? We suggest that this will be clarified. It should in any case be avoided that it would be required to perform sunset testing in situations that there is already full justification that the added test makes the to be deleted test redundant.
- 1372-1373: We find it incorrect and in fact ultimately detrimental for the quality of drugs in general to base acceptance criteria on manufacturing capability instead of on toxicity considerations. Such an approach promotes poor quality and is a disadvantage for manufacturers with the highest quality products and the best manufacturing processes.**

Explanation:

A manufacturer with poor process capabilities will be allowed to have relatively wide limits for residual solvents for a certain drug substance, while for a top class manufacturer of the same drug substance these limits will be much tighter. This will have two important implications that are both to the disadvantage of the top class manufacturer:

1. Batches of a higher quality (lower residual solvent contents) than batches manufactured and released by a poor quality manufacturer - who has wider acceptance criteria! - will have to be rejected and, if possible, reworked by the top class manufacturer. This will add to its cost of manufacture and thus weaken its competitive position in the market.
2. Process- / productivity improvements at the top quality manufacturer will much more frequently result in a residual solvent level suddenly not meeting the tight limit anymore (while often other impurity levels will decrease at the same time). Getting authorizations for such types of improvements / post-approval changes is extremely hard and in API multi-customer systems usually impossible. At the same time the poor quality competitors have very large degrees of freedom to improve their processes (decrease production cost) while remaining within the set residual solvent limits and will probably not be required to obtain any FDA pre-approval at all in similar situations. This advantageous position of poor quality manufacturers regarding possibilities to decrease production cost is a severe threat to the competitive positions and therefore to the continuity of the top class manufacturers.

Conclusion:

The application of this principle would result in the gradual decrease of overall drug quality and is therefore in various respects contrary to the interest of society. We therefore recommend to set limits based on the quantitative guidance as included in the ICH Guideline on Residual Solvents (Q3C).

- 1431 We propose that "shelf-life" will be replaced by "retest period (or if applicable shelf-life)".
Reason: Retest period is normally applicable for APIs and shelf-life only if there are specific reasons (quite unstable APIs) not to apply retest period.
- 1490 For clarification purposes it would be appropriate to explain here that stress testing results are not expected for older, well-established APIs for which the degradation pattern is well known.
- 1599-1601 It should be clarified in which cases such an evaluation will be relevant and in which cases it is not. A reasonable way to limit the scope will be to restrict this to APIs directly obtained from animals or from humans.

- 1683-1685** We find this sentence a non-science based one and therefore one that would be misplaced in this Guidance. Situations are known in which drug substances form the starting point for a very long synthesis chain that at the end results in another drug substance. In those situations it will normally be a far too strict approach to impose that the starting material should be chosen even further upstream in the synthesis chain. It should be acceptable that substances in the chain downstream from the “early” drug substance can qualify as the starting material, if properly justified with the set of criteria included in this Guidance. Examples: Many step synthesis routes for the manufacture certain steroid drug substances or for certain antibiotic drug substances.
- 1806 “are” should be “is”
- 1834-1836 Synthetic steps within the route towards the starting material may be confidential information of a supplier of the starting material (or even different sequential steps in such routes may be performed by different companies). In those cases this information may be unavailable for inclusion in the submission. Therefore, the insertion of the words “if such information on the synthesis of the starting material is available” will be appropriate.
- 1856 The definition of “unspecified” should be included in the Glossary.
- 2218-2219 In a science-based approach it is not appropriate to link the stability characteristics of a drug substance to a completely unrelated characteristic such as its pharmacological activity (in this case: antibiotic activity). We therefore propose that the words “certain antibiotics” will be replaced by “certain other labile drug substances”
- 2235-2236 Definitions included in Glossaries of major Guidelines such as this one are often used as such within other context and in other documents. Therefore, the further important explanation given in the first paragraph of Attachment 1 (that a minor contribution to the structure of the drug substance is not a criterion) should be also added here.

Finally a general comment on Attachments 1 and 2: It would be appropriate if a harmonized approach on how to select the Starting Material for regulatory submissions would be pursued within the ICH program.