

# *Bulk Pharmaceuticals Task Force*

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June 17, 2004

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

**Ref: Docket Number 2003D-0571**

Dear Sir or Madame,

I am writing on behalf of the Synthetic Chemical Manufacturer's Association (SOCMA)'s Bulk Pharmaceutical Task Force (BPTF) to express members' concerns with certain sections of the Draft Guidance for Industry titled "Drug Substance – Chemistry, Manufacturing, and Controls Information." The guidance document was made available for public comment on January 7, 2004.

BPTF is an association for manufacturers of active pharmaceutical ingredients, excipients and intermediates. Our primary objective is to seek clarification of current regulatory requirements and to interact with governmental agencies on emerging issues that may impact SOCMA members. SOCMA is the leading trade association of the specialty batch and custom manufacturing chemical industry, representing 300 member companies with more than 2000 manufacturing sites and over 100,000 employees.

Comments are listed according to the document line number.

Line 186: Master Files

The use of the term Master Files (MFs) is both of surprise and concern to the BPTF. We recommend return to the term historically used by the Agency, and which appears to have now been universally adopted, namely Drug Master Files. Alternately, we note that the recently adopted European Medicines Agency (EMA) Guideline, CVMP/134/02, uses the term Active Substance Master File. If the agency wishes to harmonize with the EMA and use the term, Active Substance Master File, we would have no objection as it appropriately describes the document. In contrast, we consider the term Master File to be insufficiently descriptive.

Lines 406/436: Flow Diagram

BPTF has concern that the large amount of information required in the flow diagram will render the diagram too cluttered and less useful. Removal of non-critical process controls (line 427) is an example of information that could be eliminated.

Line 431: Flow Diagram

The Agency is requesting that an Expected Yield be provided in the process flow diagram for each reaction step. Please be advised that for many larger volume API manufacturing processes, production of intermediates is performed as a continuous operation. For a continuous process, calculation of percent yield values is not always possible. BPTF asks that

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this fact be recognized by the addition of the phrase “where appropriate” to line 431, or that this requirement be eliminated.

## Line 457/458: Manufacturing Process Controls

The requirement for inclusion of all process controls is considered to be unnecessarily burdensome, and we request that this be replaced by a directive to list only process controls relevant to the quality of the intermediate or drug substance. Wording of other sections of the Guidance (e.g. line 538/541) should be revised to reflect the need for only critical process controls to be described.

## Lines 510/511: Process Controls

The unqualified requirement for inclusion of information on environmental controls is of concern. We note that the guidance does not restrict this requirement to sterile API or aseptic packaging operations, where environmental control is essential, or restrict the requirement to the manufacturing stage for the final API. As the agency is aware, early stage reactions are often performed in outside facilities, in closed reactors, thereby rendering environmental controls irrelevant.

As written, the Guidance could be interpreted to require that environmental controls be specified for all stages of the process. We propose that the requirement for environmental controls be qualified by, at minimum, the addition of the phrase “when appropriate” in lines 510/511; or alternatively, that further directive be provided as to when environmental controls are expected to be reported in Master Files.

## Lines 681/698: Starting Materials

The Guidance informs that “for application purposes, starting materials mark the beginning of the manufacturing process described in an application”, and also advises that “the starting material for application purposes can differ from the active pharmaceutical ingredient (API) starting material”.

BPTF agrees with the above statements, but not with the inclusion of the subsequent statement (lines 688/689) that “in general, the starting material and API starting material should be the same for a synthetic drug substance”. We purport that this statement is in conflict with the intention of ICH Q7A, and therefore requests removal of this sentence from the Guidance document.

Attachment 1 of the Guidance details how to select the starting materials (for application purposes). Based on this guidance, it is reasonable to expect that for many applications the application starting materials and the API starting materials will not be the same.

## Line 1219/1220: Analytical Procedures from Other Published Sources

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The Guidance requires that other country's compendial analytical procedures be provided in the Master File. As the Common Technical Document can be used for submission to the regulatory authorities in Japan and the European Union as well for the United States, BPTF asks the Agency to require only a citation to the analytical procedures listed in the Japanese Pharmacopeia and European Pharmacopeia, instead of requiring reproduction of the full procedure.

## Lines 1229/1231: Validation of Analytical Procedures

The Guidance states that validation information should be provided for all analytical procedures listed in the specification. It has been previously accepted that compendial or other FDA-recognized standard reference analytical methods need only be qualified as applicable. BPTF asks that the Guidance wording recognize this exemption.

An explanation is requested from the Agency as to the meaning and relevance of the following statement in the context of validation of analytical procedures:

“Stability data (S.7.3), including data from stress studies, should be used to support the validation of the analytical procedures”. Alternatively, revise the sentence to: “Stability data (S.7.3), including data from stress studies, should be used to support the validation of stability-indicating analytical procedures”.

## Lines 1683/1685: Attachment 1

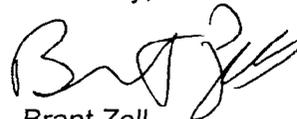
In the section titled “Starting Materials for Synthetic Drug Substances”, the Agency informs that “A drug substance that is used to synthesize another drug substance is not an appropriate candidate for designation as a starting material.” If the Agency has reviewed the Master File for the starting drug substance, we do not understand why it would not be considered a suitable candidate as a starting material. Therefore, we respectfully request that the Agency consider deleting, or at least qualifying, the wording in the quoted sentence.

## Lines 1768/1773: Attachment 1

The requirement that starting materials be “isolated and purified” is considered to be overly restrictive and potentially exclusionary in the choice of such materials.

We appreciate the opportunity to express our views on this matter.

Sincerely,



Brant Zell  
Chairman, BPTF

CC: BPTF membership  
J. Acker, SOCMA