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

Re: Draft Guidance for Industry on BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Post-approval Changes: Chemistry, Manufacturing, and Controls Documentation [98D-0994]

Dear Sir or Madam:

On behalf of the Science Committee of the Generic Pharmaceutical Industry Association (GPIA), I would like to submit comments to you on "Draft Guidance for Industry on BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Post-approval Changes: Chemistry, Manufacturing, and Controls Documentation", 63 FR 229, November 30, 1998.

GPIA is comprised primarily of manufacturers of generic medicines and suppliers of bulk active drug substances, as well as providers of technical services, to these firms. Most of our members will be directly impacted by the implementation of the subject guidance.

We, therefore, respectfully submit the attached comments prepared by a special taskforce of the GPIA Science Committee. Members of this taskforce represent both product manufacturers and bulk active substance suppliers, and foreign as well as domestic interests.

We would appreciate careful consideration of these comments as the draft guidance is finalized.

Sincerely,

Alice E. Till

Alice E. Till, Ph.D.
President

Cc S. Hyden, Chair GPIA Science Committee
L. Lin, Chair BACPAC I Taskforce
K. Srinivasachar, CDER, FDA

98D-0994

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RESPONSE TO FDA
DRAFT "GUIDANCE FOR INDUSTRY BACPAC I:
INTERMEDIATES IN DRUG SUBSTANCE SYNTHESIS (NOVEMBER 1998)
BULK ACTIVES POSTAPPROVAL CHANGES:
CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

The Generic Pharmaceutical Industry Association (GPIA) would like to take this opportunity to comment on the Draft "Guidance for Industry - BACPAC I: Intermediates in Drug Substance Synthesis (November 1998)". We appreciate the efforts put forth by the BACPAC Work Group of the Drug Substance Technical Committee and the directions provided by the CDER/CMV Chemistry & Manufacturing Controls Coordination Committee. We think this is a useful guidance to the industry and agree with many aspects of FDA's current thinking on postapproval changes for the manufacture of intermediates in drug substance synthesis. There are, however, several parts of the documents that we believe need clarification and/or modification:

Part I. General Comments

The following general comments are applicable to several sections of the guidance:

1. Common Nomenclature

   We recommend that the standard ICH nomenclature be employed whenever possible. For example, the guidance should consider the use of the term "Active Pharmaceutical Ingredient (API)" in place of "Drug Substance (DS)".

2. General Readability

   We believe BACPAC I as written can be quite confusing. It is recommended that a summary table be incorporated to ensure that the regulatory and technical requirements are clearly understood.

3. Introduction

   The guidance is focused on post-approval changes, but does not address specifically "Tentative Approvals". We recommend that BACPAC I be applied to Tentative Approvals.

4. General Considerations

   We recommend, throughout the document, to replace the requirement for "submission of at least three postmodification batches" to "submission of one postmodification batch" in all cases where equivalence is demonstrated in the final Drug Substance when compared to a sufficient range of premodification historical data. We further recommend a DMF filing requirement of ONE batch covering BACPAC I changes which result in equivalence, allowing an AR or CBE submission by the applicant. We support the recommendation with the following comments:

   A) As FDA correctly pointed out in BACPAC I (lines 57 thru 59): "This guidance is limited to changes made up to and including the final intermediate because these early modifications are generally viewed as less likely to have an adverse impact on the drug substance and, consequently, on the finished dosage form."

B) "BACPAC", referring specifically to post-approval changes, is expected to carry the assurance that the manufacturing process of the final Drug Substance has been validated, prior to the proposed post-approval change(s).

C) The process validation and original development work (premodification) carry with it, the manufacturer's understanding of the synthesis, equipment and final drug substance.

D) Actual implementation of a BACPAC I change (in one batch) carries with it prior evaluation of the intended change by the DS manufacturer, an understanding of the process, a high degree of assurance that the proposed change will not have an adverse impact on the drug substance and consequently, the finished dosage form, and equivalence is intended to be demonstrated. The focus, should therefore, not be on repetitive batches, but rather the manufacturer's ability to confirm equivalence in the post-modification batch.

E) As FDA points out in lines 167 thru 172, "pilot batches" can be used to demonstrate equivalence, allowing the "commercial batch data to be kept on file at the manufacturing site". Yet, Scale Changes (lines 286 thru 291) require submission of three postmodification batches in the new scale.

F) The BACPAC I document should clearly state that the pre-change process has been validated and used as the comparison for equivalence in the ONE post-change batch (including other batch history – when available). The document appears to cover "pilot" batches or other instances where the DS could potentially NOT have been previously validated, which is why written confirmation needs to be included clearly covering requirements for a pre-change validated process vs. one which may not have been validated.

G) To imply that three post-change batches are a DMF filing requirement is an unnecessary burden, particularly when the DMF itself (pre-change) requires batch data for one lot (e.g. Master Batch Record and Executed Batch record).

H) BACPAC I covers changes which are least likely to impact the final drug substance and include a requirement for equivalence (at the stage of change, when possible and in the final DS). As such, this document is meant to provide for a less burdensome method of filing, which is not achieved when requiring submission of data for 3 post-change batches. That requirement (for 3 batch data) would be more appropriate when considering changes to be covered under BACPAC II.

Part II. Specific Comments

The following specific comments are identified with the page number and line numbers in the draft guidance:

I. INTRODUCTION

Comment #1: Page 1 Lines 7 - 8

We suggest that the word "used" be inserted after "intermediates" to clarify the relationship of intermediates to the synthetic pathway.

Comment #2: Page 2 Lines 21 - 24

We suggest that the phrase "for specified postapproval changes" be moved after the word "information" to improve clarity of the sentence.

Comment #3: Page 3 Lines 38 - 39

For clarity, we suggest that the sentence "For changes files as a *changes being effected supplement* (21 CFR 314.70(c) and 514.8(d)(3)), the FDA may, after a review of the supplemental information, decide that the changes are not approvable." be modified to read:

"For changes files as a *changes being effected supplement* (21 CFR 314.70(c) and 514.8(d)(3)), if the Agency does not think the data provided have met the CBE filing requirements, the FDA will notify the firm within 30 days that the changes cannot be implemented as such until a supplemental application is submitted and approved by the Agency. Justification for rejecting the CBE will also be provided."

II. GENERAL CONSIDERATIONS

Comment #4: Page 3 Line 57

It is recommended that the phrase "changes made up to and including the final intermediate" be changed to read "changes made up to and including the step that produces the final intermediate". This will make it consistent with the phrase "changes involving the synthetic steps up to and including the step that produces the final intermediate" on Page 2 Lines #14 - 15.

Comment #5: Page 3 Line 77

It is recommended that the phrase "and provide confirmation that the requirements of BACPAC I have been met" be inserted between the phrases "the type of filing recommended" and "for their respective drug applications".

III. ASSESSMENT OF CHANGE

Comment #6: Page 5 Lines 123 - 124
Since these early modifications generally are less likely to have an adverse impact on the API, and consequently, on the finished dosage form, it is recommended that the following sentence: "The level of impurities should be assessed by comparing three postmodification batches to the range of historical data from ten premodification batches." be changed to read: "The level of impurities should be assessed by comparing one postmodification batch to the range of historical data from 3 - 10 premodification batches."

Comment #7: Page 5 Lines 128 - 129
It is recommended that the following phrase: "The impurity profile will be considered equivalent after a given change if at least three postmodification batches of either an isolated intermediate or the drug substance are evaluated....." be changed to read: "The impurity profile will be considered equivalent after a given change if one postmodification batch of either an isolated intermediate or the drug substance is evaluated.... ".

III-A. Equivalence of Impurity Profiles

Comment #8: Page 5 Lines 131 - 140
In addition, it is recommended that a provision (like the one shown below) be added to the end of this paragraph to allow for good science as appropriate: "When equivalence of impurity profiles in the final intermediate cannot be demonstrated, equivalence of the impurity profiles in the API should be well characterized to ensure that the observable differences in the final intermediate do not carry over into the API."

Comment #9: Pages 5 - 6 Lines 143 - 147
For clarity and ease of use of this guidance, it is recommended that key points of the applicable parts of ICH guidance Q3A *Impurities in New Drug Substances* be spelled out here.

Comment #10: Page 6 Line 152
It is suggested that the phrase "the stated limits" be changed to "the established limits".

Comment #11: Page 6 Lines 167 - 168
It is recommended that the bullet statement: "Changes in process, specifications, or equipment may be evaluated using data from pilot scale batches. If equivalence is demonstrated by using pilot batches, the first commercial batch should also be evaluated for equivalence." be changed to read; "Changes in process, specifications, or equipment may be evaluated using data from postmodification pilot scale batch(es). If equivalence is demonstrated by using pilot batch(es), the first commercial batch should also be evaluated for equivalence."

III-B. Equivalence of Physical Properties

Comment #12. Page 7 Lines 188 - 191
It is recommended that the phrase "the possibility of such changes in physical properties should be considered" be changed to "the possibility of such changes in physical properties should be considered and verified if appropriate".

The phrase in the last sentence: "unless equivalence of the impurity profile can be demonstrated prior to or at the final intermediate" should also be deleted.

Comment #13. Page 7 Line 194 - 196
It is recommended that the sentence: "The physical properties of the drug substance will be considered equivalent after a given change if at least three postmodification batches of the drug substance are prepared" be changed to read: "The physical properties of the drug substance will be considered equivalent after a given change if one postmodification batch of the active pharmaceutical ingredient is prepared".

IV. TYPES OF CHANGE

IV-A. Site, Scale, and Equipment Change

1. Site Changes

Comment #14: Page 9 Line 241
It is recommended that the phrase "data on at least three batches" be changed to "data on at least one batch".

2. Scale Change

Comment #15: Page 10 Line 287
It is recommended that the phrase "data on at least three batches" be changed to "data on at least one batch".

IV-B. Specification Changes

2. Other Specification Changes

Comment #16: Page 14 Line 372
It is recommended that the phrase "data on at least three batches" be changed to "data on at least one batch".

Comment #17: Page 14 Line 375
It is recommended that the phrase "Validation data" be changed to "Method validation data".

Comment #18: Page 14 Lines 397 - 398
The sentence: "In those situations, the appropriate review division(s) should be contacted for concurrence." should be deleted.

IV-C. Manufacturing Process Changes

1. Changes That Do Not Involve New Starting Materials or Intermediates

Comment #19: Page 14 Line 406
In order to provide guidance to the industry with regard to changes in catalysts, it is recommended that the word "catalysts," be inserted between "reagents," and "process parameters".

Comment #20: Page 15 Line 415
It is recommended that the phrase "data on at least three batches" be changed to "data on at least one batch".

Comment #21: Page 15 Line 417
It is recommended that the phrase "Validation data" be changed to "Method validation data".

2. Changes in the Route of Synthesis in One or More Steps Involving Different Starting Materials and/or Intermediates (except the final intermediate)

Comment #22: Page 16 Line 454
It is recommended that the phrase "data on at least three batches" be changed to "data on at least one batch".

Comment #23: Page 16 Line 456
It is recommended that the phrase "Validation data" be changed to "Method validation data".

3. Changes in which an Intermediate Is Redefined as a Starting Material

Comment #24: Page 17 Line 502
The "," at the end of the sentence should be deleted.

Comment #25: Page 18 Line 508
It is recommended that the phrase "data on at least three batches" be changed to "data on at least one batch".

Comment #26: Page 18 Line 511
It is recommended that the phrase "Validation data" be changed to "Method validation data".

ATTACHMENT B. GLOSSARY OF TERMS

Comment #27: Pages 22 - 24 Lines 568 - 644
(General Comment)
We suggest that the common glossary of terms shown in Attachment B be compared against the definitions listed in the March 1998 FDA Draft Guidance for Industry "Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients" for consistency.

Comment #28: Page 22 **Drug Substance** Line 576
It is recommended that the term and description of "Drug Substance" be replaced by "Active Pharmaceutical Ingredient".

Comment #29: Page 22 **Final Intermediate** Lines 580 - 584
It is recommended that the following sentence be added to the end of the description: "In a convergent synthesis - in which two isolated intermediates are being reacted together to form the API molecule - both intermediates would be defined as final intermediates."

Comment #30: Page 22 **Historical Data** Line 589
It is recommended that the phrase "10 recent batches" be changed to "3 - 10 batches".

Comment #31: Page 24 Lines 628
It is recommended that the term and description of "Raw Material" be inserted here. We believe the definition given in the March 1998 FDA Draft Guidance for Industry "Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients" is adequate:

Raw Material: Any ingredient intended for use in the production of APIs. These may include starting materials, process aids, solvents, and reagents.

Comment #32: Page 24 Lines 628 -630
It is recommended that the term and description of "Synthetic Drug Substance" be replaced by "Synthetic Active Pharmaceutical Ingredient".