Aventis Pharmaceuticals

Aventis

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November 20, 2001

Via fax and UPS

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

Re: Docket No. 01D-0361
Draft Guidance: ICH Q1D Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products [66FR 49029, September 25, 2001]

Dear Sir/Madam:

Aventis Pharmaceuticals would like to thank you for the opportunity to comment on the above-referenced Draft Guidance entitled "Q1D Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products". The document provides guidance on the application of reduced designs (i.e. bracketing and matrixing) for stability studies conducted in accordance with the principles outlined in the revised guidance entitled "Q1A(R) Stability Testing of New Drug Substances and Products". The development of this ICH Q1D draft guidance on bracketing and matrixing is welcomed. The underlying principles are generally sound and acceptable. We offer the following comments/clarification for your consideration.

1. INTRODUCTION

1.1 Objectives of the Guideline

Page 2 – Line 13 to 16

The objective of this guideline is to provide harmonised guidance on the application of bracketing and matrixing for stability studies conducted in accordance with principles outlined in the ICH Q1A Harmonised Tripartite guideline covering Stability Testing of New Drug Substances and Products (hereafter referred to as the parent guideline).

Q1A is referred to as "the parent guideline", but this has been superseded by its revised version, **Q1A(R)**, published in the Federal Register on November 7, 2001. Therefore, this should be cross-referenced.

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1.2 Background

Page 2 – Line 20 to 21

Q1A notes that the use of matrixing and bracketing can be applied, if justified, to the testing of new drug substances and products, but provides no further guidance on the subject.

Since the revised version Q1A(R) should be referred to as the parent guideline (as indicated in 1.1), we suggest replacing "*Q1A*" with "**The parent guideline** notes that ...".

2. GUIDELINES

2.1 General

Page 3 – Line 42 to 44

Any reduced design should retain the ability to adequately detect differences in stability resulting from any of the design factors.

We believe that this statement requires further clarification and suggest phrasing this requirement such that this evaluation should be done relative to the full design. We propose rewording this sentence as follows: "*Any reduced design should retain the* **adequacy relative to a corresponding full design to** *detect differences in stability resulting from any of the design factors.*"

Page 3 – Line 44 to 45

Before a reduced design is considered, certain assumptions should be assessed and justified.

We believe that clarification should be provided as to what the "*certain assumptions*" refer to. Otherwise, this sentence should be deleted.

2.2 Applicability of reduced Design

Page 3 – Line 65 to 66

Bracketing and matrixing are reduced designs based on different principles. Therefore, the use of bracketing and matrixing together in one design should be considered and scientifically justified.

To make this statement clearer, we propose the following wording "*Therefore,* **careful consideration and scientific justification should precede** *the use of bracketing and matrixing together in one study.*"

2.3 Bracketing

Page 3 – Line 73 to 81

As defined in the glossary to the parent guideline, bracketing is the design of a stability schedule such that only samples on the extremes of certain factors, e.g., strength, package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes of or different fills in the same container closure system.

There is some duplication with section 2.3 that could be consolidated. Therefore, we suggest deleting the third and fourth sentence in this paragraph (line 76 to 81) "*Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes of or different fills in the same container closure system.*"

2.4 Matrixing

2.4.2 Design Considerations

Page 6 – Line 183 to 185

A matrix design should be balanced such that each combination of factors is tested to the same extent over the intended duration of the study and, as far as possible, at the intended submission time.

We believe that this requirement is unnecessary and would lead to some strange anomalies. For example, a matrix design that is balanced could be augmented by running additional samples that would give more information but was no longer balanced. This requirement would permit the smaller study, but exclude the larger study which included the original design as a subset. Strangely, the examples given in table 2 & 3 are not balanced as stated here (unless balance over time is not deemed necessary). We would suggest adding a statement that "**deviations from the balanced design are acceptable with justification.**" We believe the issues relevant to this point are already discussed in section 2.4.5.

2.4.3 Example Designs
2.4.3.1 Simple Designs
Page 7 - Table 2 One Half reduction

The example given in Table 2 One Half reduction are not of a particularly good design. For example, the test point for strength S1, batch 3, time 24 months should be made at 18 months; with this design three tests will be performed at all time points.

2.4.3.2 Complex Designs
Page 8 - Table 3b Incomplete design

Since an incomplete design using a one third reduction is given as an example in Table 3b, "*T1*" for the strength S1, container size B and batch 3 would need to be deleted in this table.

2.4.4 Applicability and Degree of Reduction
Page 8 – Line 260 to 262
A statistical justification could be based on an evaluation of the proposed matrix design with respect to its power to detect differences among factors in the degradation rates or its precision in shelf life estimation.

We believe that this statement requires further clarification and suggest phrasing this requirement such that this evaluation should be done relative to the full design. We propose rewording this sentence as follows: "*A statistical justification could be based on an evaluation of the proposed matrix design* **relative to the full design** *with respect to its power to detect differences among factors in the degradation rates or its precision in shelf life estimation.*"

Page 8 – Line 269 to 270
Any matrix design should retain an adequate ability to detect stability differences within factors or among factors.

We believe that this statement is a reiteration from earlier in the draft. Therefore we suggest deleting this last paragraph (line 269 to 270).

Finally, even though this draft guidance Q1D, and its parent guidance Q1A(R) address the information to be submitted in registration applications for new molecular entities and associated drug products without covering specific details for particular dosage forms, we would like to emphasize that bracketing and matrixing should be encouraged for stability studies with nasal and oral inhalation products. There is no significant differences between these dosage forms and others for which the industry and authorities would routinely accept reduced stability design.

On behalf of Aventis Pharmaceuticals we appreciate the opportunity to comment on Q1D Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products and thank you for your consideration.

Sincerely,

Steve Caffe, MD
Vice President, Head GRAMS – North America
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FAX

Date: November 20, 2001

Number of pages including cover sheet: 6

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REMARKS: ☐ Urgent ☐ For your review ☐ Reply ASAP ☐ Please comment

Dear Sir/Madam:

Attached please find comments regarding "Draft Guidance: ICH QID Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products" [66FR 49029, September 25,2001].

Should you have any questions, please call me at your convenience.

Regards,

Jackie Knoble