3M Pharmaceuticals

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November 26, 2001

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3M

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

Re: Docket No. 01D-0361
Comments on the Draft Guidance on ICH Q1D Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products

Dear Sir or Madam:

On behalf of 3M Pharmaceuticals, I am writing to register comments to Docket Number 01D-0361on the ICH Draft Guidance entitled *Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products*, dated November, 2000. The availability of this document was published in the Federal Register on September 25, 2001 as a Notice. The comments begin on the next page.

Should you have any questions regarding the comments, please don't hesitate to call me at (651) 736-1590.

Sincerely,

Amy E. Fowler

Amy E. Fowler
Senior Regulatory Associate

01D-0361

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3M Pharmaceuticals' Comments to FDA's draft guidance entitled

Q1D: Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products

General comments

This draft guideline is at Step 2 of the ICH process. Concern is raised that if the FDA guidance is finalized prior to completion of the ICH process, the ICH and FDA instructions on this topic could differ.

Specific dosage forms to which this guidance applies have not been listed. It is recommended that the relevant dosage forms be listed within the scope of the guideline to ensure that NDA sponsors and the FDA review divisions are clear on what product types can and cannot be supported with this guidance. This is a suggestion to ensure work done by an NDA sponsor to justify a matrixing or bracketing regimen will be thoughtfully considered and responded to by the FDA.

The logistics and timing of proposals to the FDA have not been discussed in the guidance document. It is requested that suggested timings and meetings be discussed in the document. For example, is it the intention that the NDA sponsor would provide the proposals at the entitled End of Phase 2 meeting or shall a separate Type C meeting or teleconference be called? Also, information in the guidance on the expected amount of time to receive feedback from the FDA on the proposal will be necessary for the NDA sponsor to incorporate the FDA's suggestions.

The guidance suggested approach to matrixing addresses the option of not conducting tests at selected time points. Under this proposal all batches would be tested for all test parameters at the designated time points. Please consider the approach of matrixing both batch and test parameters to allow a reduced testing plan for the NDA sponsor but yet full product characterization for key tests or trending parameters. For example, if the test results for a particular parameter do not trend and the product is well characterized for

this parameter, testing on all three batches of a particular size and strength is not required. However, the NDA sponsor could generate data on a "reduced testing batch" for a trending or otherwise non-linear test parameter to secure test data on at least three batches of each container and fill size to support expiry and stability assessments.

Several references are made to matrixing test attributes as well as (or rather than) time. Please provide clarification beyond "if justified."

Specific comments

Lines 83/84:
The use of a bracketing design would not be appropriate if it cannot be demonstrated that the strengths or container sizes and fills selected for testing are indeed the extremes.

Please clarify what is meant. For example, does this refer to the product composition or a product performance characteristic?

Lines 99/100:
.....where the relative amounts of drug substance and excipients change in a formulation.

Please provide guidance on the degree of a shift in relative amounts that would be acceptable/unacceptable.

Lines 158/159:
Matrixing should not be performed across test attributes. However, alternative matrixing designs for different test attributes can be applied, if justified, with different testing frequencies.

It is suggested that once product stability has been established, it is not necessary to conduct every test point for a non-trending parameter. Hence, please consider the allowance to matrix without justification for parameters that are not trending.

Lines 193-195:

For matrixing at an accelerated or intermediate storage condition, care should be taken to ensure testing occurs at a minimum of three time points, including initial and final, for each selected combination of factors.

Should the three timepoints required by the parent guideline be for the same product batch? If so, then matrixing would not be an option for accelerated stations. We assume that time-based matrixing at accelerated stations is valid only where variability and stability are good. Please clarify.

Lines 214-217:

In Table 2, "One half reduction," there are two points under 18 months, but four points under 24 months. Should there be three points under each instead?

Lines 241/242, the Table "3b Incomplete design":

Based on the logic of this incomplete design utilizing testing for only two lots per strength and container size, it is assumed that the third column in the table has a mistake. That column refers to S1, container size B. The assumption is that the "T1" in the last row for Batch 3 should not be included. Hence, only Batch 1 will be tested to the "T2" schedule and Batch 2 will be tested to the "T3" schedule.

Lines 255-258. The guidance suggests that if supporting data indicate small variability and excellent product stability, a statistical justification to matrix is not required. The assessment of small variability and excellent product stability can be subjective and as such a statistical assessment should be provided with each proposal to matrix. Variability assessments are based on the amount of variability the data exhibits in comparison to the intended specification at product expiry. The specification and expiry may not be known at the development stage of a product.

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