

# Genentech, Inc.

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May 31, 2000

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

Re: Docket No. 93D-0139  
ICH Draft Revised Guidance on Q1A(R) Stability Testing of New Drug Substances and Drug Products

I would like to submit the following comments to the revised draft guidance:

Supplementary Information, paragraph 9: It is stated that this draft guidance applies in general to biotechnological/biological products and that specific guidance for such products may be found in Q1C and Q5C. Since there are several key differences between these guidance documents relative to filing requirements, please clarify if and when Q1A should be interpreted to take precedence over Q1C or Q5C.

Drug Substance; Test Attributes, ..., paragraph 3: It is stated that acceptance criteria should include limits for "impurities and degradation products". Use of the term "impurities" (as defined in Q6B) is redundant here, since only those impurities that form or increase over time (i.e., degradation products) will be monitored in a stability program.

Drug Substance; Testing Frequency, paragraphs 2 and 3: It should be clearly stated that the total duration of testing for the accelerated and intermediate conditions for the general case is 6 and 12 months, respectively.

Drug Substance; Storage Conditions, paragraph 2: Is 12 months of stability data needed for all three lots or just the oldest lot? Please clarify.

Drug Substance; Storage Conditions; Drug Substances Intended for Storage in a Freezer: The following statement should be added: "For manufacturing operations that require a frozen drug substance to be thawed, aliquoted, and the remainder refrozen one or more times, data should be provided on a single batch of drug substance to show that it still meets the acceptance criteria following the maximum number of freezing and thawing cycles."

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Drug Substance; Evaluation, paragraph 5: It is not clear how accelerated data may be used to allow for the extrapolation of real-time data. In the absence of such guidance, accelerated data is only useful in evaluating the impact on excursions outside of recommended storage conditions (e.g., shipping). If that is the case, then requiring 6 months of accelerated data is excessive.

Drug Product; Selection of Batches, paragraph 2: The statement on unacceptability of laboratory scale batches is too restrictive and absolute. If it can be demonstrated that a batch smaller than pilot scale is representative of a production batch, as defined in paragraph 1, then its use as one of the primary lots in a formal stability study should be allowed. An example would be a manual fill of a drug substance into drug product vials under controlled laboratory conditions.

Drug Product; Packaging/Containers: The first sentence should be changed to state that the dosage form should be stored in the “container proposed for marketing”. Additionally, if the product container is semi-permeable, then stability testing should be conducted on the dosage form stored in product containers that include the secondary packaging.

Drug Product; Testing Frequency, paragraphs 2 and 3: It should be clearly stated that the total duration of testing for the accelerated and intermediate conditions for the general case is 6 and 12 months, respectively.

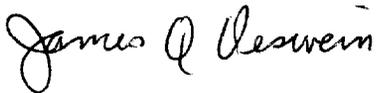
Drug Product; Storage Conditions, paragraph 3: Is 12 months of stability data needed for all three lots or just the oldest lot? Please clarify.

Drug Product; Storage Conditions, paragraph 4: A 5% change in potency may not be measurable. Many potency assays, especially those for biotechnological/biological products, typically have a precision of 10 to 20 percent. In such cases an acceptable potency range is specified which takes the assay precision into account and a significant change would be a failure to meet these acceptance criteria.

Drug Product; Stability Commitment, paragraph 7: The following sentence should be added: “If no significant changes are seen for the accelerated storage condition for the three primary batches, testing on the commitment batches should be conducted at the long-term storage condition only. In addition, one drug product batch should be placed on long-term stability annually following approval. The stability protocol used for annual, post-approval batches should be the same as that for the production batches unless otherwise scientifically justified. For example, the testing frequency for annual batches may be reduced (e.g., annual testing only) if the data from the primary and production batches clearly show that the drug product meets acceptance criteria throughout its proposed shelf-life.”

Drug Product; Evaluation, paragraph 6: It is not clear how accelerated data may be used to allow for the extrapolation of real-time data. In the absence of such guidance, accelerated data is only useful in evaluating the impact on excursions outside of recommended storage conditions (e.g., shipping). If that is the case, then requiring 6 months of accelerated data is excessive.

Sincerely,

A handwritten signature in black ink that reads "James Q. Oeswein". The signature is written in a cursive style with a prominent initial "J" and a distinct "Q".

J. Q. Oeswein, Ph.D.  
Associate Director  
Quality Control

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