

PDA's comments on:

(1) Interim Guidance, Immediate Release Solid Oral Dosage Forms, Pre- and Post-Approval Changes (SUPAC-IR)

(2) ICH Tripartite Guideline Covering Stability Testing Requirements for New Dosage Forms and for Variations and Changes to New Drug Substances and New Drug Products, Draft Number 2 (Q1C)

(3) Docket No. 93D-0403, Supplements to New Drug Applications, Abbreviated New Drug Applications, or Abbreviated Antibiotic Applications for Nonsterile Drug Products; Draft Guideline (60 FR 64093, December 12, 1994)

Explanatory note:

On December 9, 1994, FDA requested comment from industry trade organizations on the initial draft of the SUPAC-IR document and the ICH-Q1C (Stability test requirements for changes or new dosage forms). On December 12, 1994, FDA published a related draft guidance on supplements for non-sterile drugs. Following are PDA's comments on all three documents by letters of February 10, 1995 (SUPAC-IR and Q1C) and March 10 (December 12, 1994 guideline). SUPAC-IR was formally released in November 1995. ICH Q1C has been shelved indefinitely by the ICH steering committee. PDA staff contact:

James C. Lyda, x121
July 1996

February 10, 1995

Roger L. Williams, M.D.
Associate Director for Science and Medical Affairs
Food and Drug Administration
7500 Standish Place (HFD-600)
Rockville, MD 20855

February 10, 1995

Re: SUPAC-IR & ICH Q1C

Dear Dr. Williams:

Enclosed please find PDA's comments on two documents: (1) Interim Guidance, Immediate Release Solid Oral Dosage Forms, Pre- and Post-Approval Changes (SUPAC-IR), and (2) ICH Tripartite Guideline Covering Stability Testing Requirements for New Dosage Forms and for Variations and Changes to New Drug Substances and New Drug Products, Draft Number 2 (Q1C). Our Comments are submitted in response to your request at the December 9, 1994 briefing for PDA, PhRMA, and other industry groups.

Our comments on SUPAC-IR are clarifying in nature. We recommend FDA proceed with a formal issuance to the industry as quickly as practical. Our comments on Q1C relate to consistency with the parent ICH Q1A guideline, internal consistency and relationship to SUPAC-IR.

As you know, this was a group effort by PDA volunteers, and some of these comments may be reflected in correspondence from their parent companies.

I have heard nothing but positive comments regarding the December 9 briefing. The focused administration of the meeting combined with the quantity and quality of information provided was impressive. CDER's outreach to industry for early input is very much appreciated. I trust our comments will justify your effort.

Please call me, or James Lyda of my staff, if you have any questions regarding our comments. We look forward to working with you in the same manner on future issues.

Sincerely,

Edmund M. Fry
President

cc: G. Poochikian, J. Showalter

SUPAC-IR
PDA Comments to FDA
February 10, 1995

Interim Guidance
Immediate Release Solid Oral Dosage Forms
Pre- and Post-Approval Changes
(SUPAC-IR, Draft, November 29, 1994)

GENERAL COMMENTS:

SUPAC-IR document has been well received by our task force and others familiar with its content. We recommend FDA proceed with a formal issuance to the industry as quickly as practical. We note the lack of container/closure guidance (As in ICH Q1C) but suggest such guidance can be added later and should not delay publication.

SPECIFIC COMMENTS:

Definitions: Update to reflect terms used in the document and include a definition of 'performance'.

Rationale: Clarity

Page 6: Substitute FINAL DRUG PRODUCT WEIGHT for TOTAL DOSAGE in table header and include example.

Rationale: There is confusion in the interpretation of the table and the impact these changes have on the tablet weight target.

Page 7: Delete 'accelerated stability testing' from section III A 2 a.

Rationale: Changes not likely to impact product performance should not require expanded stability studies.

Page 8: Define what is meant by 'technical grade' and substitute FINAL DRUG PRODUCT WEIGHT for TOTAL DOSAGE in table header.

Rationale: Clarity.

Pages 9 & 10: Case A & Case B should specify dissolution test parameters. For example, Case A could refer to USP dissolution parameters and Case B could refer to USP, NDA or ANDA dissolution parameters with three (3) solutions: water, 0.1 N HCL and USP buffer pH 7.5.

Rationale: Defines test parameters.

Page 10: Define what is meant by 'qualitative' excipient changes in section III C 1 a.

Rationale: Clarity.

Page 12: Level 2 change should also include contract manufacturers.

Rationale: Defines requirement for both company owned and contract facilities.

Page 13, 14 & 15: Substitute 'CHANGES IN BATCH SIZE (SCALE-UP/SCALE-DOWN)' for 'SCALE-UP' in header for section V. Replace 'scale-up' with 'scale-up/scale-down' throughout section V.

Rationale: Both increases and decreases in batch size are likely during a product's life cycle and it is reasonable that the same requirements would apply.

Page 14: Add 'pilot/' before 'biobatch' in the first sentence of section A.

Rationale: Consistency with the introductory paragraph of the section.

Page 16: Change 'Case B' to 'Case C' in section VI A 2 b.

Rationale: Reference relates to Case C.

Page 17: Delete 'Accelerated' stability in section VI B 1 a.

Rationale: Changes not likely to impact product performance should not require expanded stability studies.

Page 18: Substitute 'current revision of USP/NF' for 'USP/NF XXII'.

Rationale: This change allows the document to remain current with changes in USP/NF.

Foot Notes: Consider including footnote terms in the definitions.

Rationale: Consistency.

Possible Future Changes: The inclusion of container/closure changes similar to ICH Q1C would be helpful, but should not delay release of SUPAC-IR.

ICH Q1C
PDA Comments to FDA
February 10, 1995

ICH Tripartite Guideline
Stability Testing Requirements for New Dosage Forms and for
Variations and Changes to
New Drug Substances and New Drug Products
(Topic Q1C, Draft 2, December 15, 1994)

GENERAL COMMENTS:

A. Application of the Q1A guideline: The parent ICH guideline 'Stability Testing of New Drug Substances and Products' (Q1A) was published by FDA on September 22, 1994. The *Federal Register* notice described the document as effective that date, although FDA has explained that first conformance with the guideline will be expected only for applications covering new molecular entities submitted after January 1, 1998.

This has created confusion and regulatory expectation that changes to currently approved products should be supported by testing under ICH storage conditions such as 25°C/60% RH. This will result in a significant number of marketed products not meeting specifications previously established under lower humidity storage conditions.

B. Significant body of stability data: For products not registered under ICH 25°C 60%RH/40°C 75%RH stability storage conditions, the stability studies should be performed under the conditions (normal and accelerated) described in the registration package. This modification to the Q1C document will permit a direct comparison of the change to the original process and is consistent with the statements under "General" (lines 1 - 5.)

C. Format and Presentation of the Guideline: We recommend the EWG present the requirements of the guideline in a table or matrix format, similar to the table in the Q1A guideline.

SPECIFIC COMMENTS BY SECTION OF DRAFT 2:

1.0 General

Line 9: Delete 'regulatory'.

Rationale: In conflict with rest of paragraph which states that regulatory requirements may vary in three areas of EU, USA, Japan.

2.0 New Dosage Forms

Editorial Note 1: Lines 10 - 14 appropriately describe the requirements for New Dosage Form.

Editorial Note 2: Delete this definition, lines 10 - 14 are more appropriate.

3.0 Variations & Changes

Line 15: Delete 'assumed'.

Rationale: Not required.

Line 16: Delete 'commercial'.

Rationale: Consistent nomenclature with parent stability guideline.

Line 17: Delete 'marketed in the region where the drug application is filed'.

Rationale: The inherent stability of a drug substance/drug product is independent of where it is sold. The basic premise of the ICH is that data is acceptable in all three areas EU, Japan, USA.

Line 21: Delete 'commercial'.

Rationale: Consistent nomenclature with parent stability guideline.

Editorial Note 3: 'Significant body of data' should be defined as 12 month data on 3 production batches.

Line 45: Delete 'commercial'.

Rationale: Consistent nomenclature with parent stability guideline.

Editorial Note 4: A prescriptive definition is preferred to an open ended or subjective description.

Editorial Note 5: Delete lines 64 and 65. As described in lines 6 - 9, this guideline is not intended to describe the regional regulatory requirements.

Editorial Note 6: Photostability requirements should be described in the photostability annex. The sentence as written is adequate.

Line 64: See Editorial Note 5. If this line is retained, delete 'commercial'.

Rationale: Consistent nomenclature with parent stability guideline.

3.2 Change in the Manufacturing Process of the Drug Substance:

Note: If a multi-step synthetic process is used to manufacture the drug substance, a statement is needed to clarify that changes in the process prior to the pivotal intermediate (sometimes called "the GMP step") need not comply with this guideline.

Line 72: Delete 'commercial-size'.

Rationale: Inconsistent with lines 44 - 47 and the parent stability guideline which only requires 3 pilot lots to approve the original application for a new drug substance.

Line 80: Delete 'commercial'.

Rationale: Consistent nomenclature with parent stability guideline.

Lines 83 - 85: Delete this sentence.

Rationale: This sentence is redundant and less specific than statements in lines 56 - 63 above.

3.3 Significant Change in Formulation of the Drug Product

Line 87: Change 'might be expected' to 'is likely'.

Rationale: For consistency with SUPAC-IR Level 3 definition.

Line 93: Add 'as demonstrated in the original product stability profile' after the words '5 per cent' and before 'then six months....'.

Rationale: To be consistent with paragraphs 38 - 43. Or, delete sentence in lines 91 - 94 entirely since previously stated (lines 38 - 43).

Editorial Note 7: Definition of minor formulation changes in this annex with examples would be helpful. However, the stability testing requirements for these should also be included. This would create more consistency with SUPAC guidelines.

3.4 Addition of a New Strength for the Drug Product

Editorial Note 8: Paragraph (lines 109 - 112) is appropriate as written for this annex.

3.5 Changes in Container and Closure of the Drug Product

Line 113: The exact meaning is unclear, in particular 'unless otherwise noted'.

Lines 113 - 116: This paragraph is redundant and less specific than statement in lines 56 - 63 above.

3.5.1 Addition of a New Pack

Editorial Note 9: Although scientifically a sound experimental design, it may not be practically feasible. Packaging component fabricators routinely purchase raw materials in quantities that encompass many batches of fabricated components. Therefore, variability from batch-to-batch of packaging components will likely be due to physical parameters. These types of variations are better determined by physical testing of the package versus the specifications.

3.5.2 Changes in Container or Closure Type

Line 129: Same comment as Editorial Note 9.

Lines 130 - 132: Delete.

Rationale: Should be consistent with lines 56 - 61.

Lines 133 - 135: Clarify wording 'for submission to the pertinent regulatory authorities as specified.' As specified by what or whom?

Rationale: Requirements not specified.

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March 10, 1995

US Food and Drug Administration
Dockets Management Branch (HFA-305)
12420 Parklawn Drive, rm 1-23
Rockville, MD 20857

Re: Docket No. 93D-0403
Supplements to New Drug Applications, Abbreviated New Drug Applications, or Abbreviated Antibiotic Applications for Nonsterile Drug Products; Draft Guideline (60 FR 64093, December 12, 1994)

Dir Sir or Madam:

The Parenteral Drug Association (PDA) is offering comments on the above draft guideline. The comments were prepared by a committee of volunteer members of the association and PDA's professional staff.

SUPAC-IR¹ and ICH Q1C². On February 10, 1995 PDA provided comments supporting CDER issuance of SUPAC-IR. On the same date PDA provided technical comment on ICH Q1C (see enclosures). This was in response to CDER's briefing of December 9, 1994. Comments were submitted to Dr. Roger Williams, Associate Director for Science and Medical Affairs, CDER.

Scope of Guidance. The three documents can be organized in a hierarchy based on scope of guidance, with SUPAC-IR the narrowest and ICH Q1C the broadest:

Draft Document	SUPAC-IR	December 12, 1994 Guideline	ICH Q1C
Scope of Guidance	Solid oral dosage forms, immediate release drugs	All nonsterile drug products	All dosage forms, sterile and nonsterile, and all drug substances

Overlap of content. Although the content and structure of these three documents are different, there is some degree of overlap, particularly between SUPAC-IR and the December 12 draft, both of which are FDA drafts. Our task force prepared a matrix comparison of the drafts based on the type of change being considered by the manufacturer or applicant. We have enclosed a copy of that matrix for FDA use as your revision of the documents proceeds.

Please keep in mind that the matrix represents our best understanding of how the documents relate to each other, and we may well have misunderstood some provision or requirement. All three documents are, after all, still in draft.

Impact on December 12 draft. It is our understanding that CDER is committed to finalization of the SUPAC-IR guidance in the very near future. Similarly, ICH Q1C will be the focus of continued FDA commitment when the ICH Steering Committee and Expert Working Groups meet in late March 1995.

Clearly, the final content of the December 12 draft will be influenced by the final revisions of SUPAC-IR and ICH Q1C.

Recommendation. PDA recommends that FDA reconsider the content, structure, and terminology in this draft guideline in the context of the SUPAC-IR and ICH Q1C guidance. All three documents (if three are indeed needed) should be in harmony with each other when they are final. Since the next draft of this guideline may be quite different from this version, we request the FDA again publish it for comment.

Please contact me, or James C. Lyda of the PDA staff, if you have any questions.

Sincerely,

Edmund M. Fry
President

cc: Roger Williams, M.D.
Janet Showalter

About PDA. The Parenteral Drug Association (PDA) is an international association for pharmaceutical science and technology founded in 1946 and specializing in quality assurance and manufacturing issues for pharmaceuticals, biopharmaceuticals and related health care products. Our 6,500 worldwide members include scientists and technical representatives of manufacturers, regulatory officials, members of academia and suppliers of equipment and services.

PDA SUPAC/ICH Post-Approval Task Force

PDA thanks the following experts for their assistance in preparing comments on all the above documents:

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1. Interim Guidance, Immediate Release Solid Oral Dosage Forms, Pre- and Post-Approval Changes (SUPAC-IR), FDA/CMC CC, November 29, 1994

2. ICH Tripartite Guideline Covering Stability Testing Requirements for New Dosage Forms and for Variations and Changes to New Drug Substances and New Drug Products, (Q1C) Draft Number 2, International Conference on Harmonization, December 15, 1994