

Common Drug Product Quality Issues and How to Mitigate/Avoid Them

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Pharmaceutical Quality




A quality product of any kind consistently meets the expectations of the user.



Drugs are no different.



**Patients expect safe and effective medicine
with every dose they take.**

A close-up photograph showing a hand holding an orange plastic pill bottle, tilted to pour three white, oval-shaped capsules into the palm of another hand. The background is blurred, focusing on the action of dispensing the medication.

Pharmaceutical quality is
assuring *every* dose is safe and effective,
free of contamination and defects.



It is what gives patients confidence in their *next* dose of medicine.

Objectives

- Discuss common deficiencies in drug product specifications (Section P.5 of global submit)
 - Description
 - Assay
 - Organic Impurities (Covered by ICH Q3A, Q3B, USP)
- Discuss common deficiencies in drug product stability (Section P.8 of global submit)
- Provide points to consider when responding to the deficiency letter
- Case study, Poll Question

Description/Appearance

- Acceptance Criteria (AC): Product specific
- **Common Deficiency**
 - X Failure to include AC for product integrity (defects) in specification

Deficiency

“OPQ defines quality of drug product as free of contamination and defects. Thus, we recommend that you include a statement “free from physical defects” in the “Description” of your drug product specification at release and stability”.

References: ICH Q6A and USP General Chapter <2>

Assay

- Acceptance Criteria:
 - 90% - 110% of Label claim
 - 95% - 105% of label claim for products with narrow therapeutic index (NTI)
- **Consideration:**
 - ✓ Base on ICH Q6A, a tighter limit for release specification may be recommended as control to ensure quality throughout the drug product shelf life.

Deficiency

Based on ICH Q6A, a tighter limit may be recommended at release as a control to ensure that the product will remain within the regulatory acceptance criterion throughout its shelf life (regulatory specification).

References: USP General Chapter <2>, Product specific USP monograph and ICH Q6A

Organic Impurities

(Covered by ICH Q3A, Q3B and USP monograph)

- Specified Degradation Products
 - Specified Identified Degradation Products
 - Specified Unidentified Degradation Products
- Any Unspecified Degradation Product
- Total degradation products

References: ICH Q6A, ICH Q3B, MaPP 5017.2 and Product specific USP monograph

Degradation products

- Limits for degradation products:
 - Drug product specific USP monograph
 - ICH Q3B:

Degradation Product	Qualification Threshold (QT)	Identification Threshold (IT)
Specified <u>Identified</u> Degradation Product	√	-
Specified <u>Unidentified</u> Degradation Product	-	√
Any <u>Unspecified</u> Degradation Product	-	√

Degradation products

- **Common deficiencies:**

- X Including process impurity (non-degradation product) of drug substance in drug product specification at ICH Q3B QT
- X The limit for “any unspecified degradation product” is above ICH Q3B IT
- X Failure to identify/control all known degradation products

Deficiency

Please comment upon the potential formation of the following degradation product (chemical structure shown in deficiency letter). Based on your assessment, please add a control for this impurity (degradation product) to the drug product release and stability specifications as applicable. In addition, please update method validation report (if applicable) to demonstrate suitability for detection and quantification of this potential degradation product.

Individual Specified Degradation products

- Specified impurity with a proposed limit above the QT is considered qualified if:
 - ✓ USP monograph recommends a limit above QT
 - ✓ Data from nonclinical studies, publicly available information or toxicology studies
 - ✓ Comparison to the RLD using the same method of analysis
- **Common deficiencies:**
 - X Failure to justify proposed limit above the QT for degradation product
 - X Failure to justify that degradation product is a human metabolite
 - X Failure to adequately compare the impurity in ANDA product to that in RLD

References: ICH Q6A, ICH Q3B, Product specific USP monograph

Total degradation products

- The total degradation products:
 - ✓ Sum of acceptance criteria for individual specified (identified and unidentified) degradation products (MaPP 5017.2)
- Considerations:
 - Significant human metabolites should be excluded
 - The limit for the sum of all impurities (including metabolites) vs. Potency/Assay through product expiry
- **Common deficiency:**
 - X Failure to justify proposed limit for Total degradation products

Deficiency

Manual of Policies and Procedures, MaPP 5017.2 (Section 2.1 under Policy) recommends that the limit of total impurities should not exceed the summation of acceptance criteria for individual specified impurities. Please revise the limit of total impurities in your drug product specifications accordingly

References: MaPP 5017.2, ICH Q6A, ICH Q3B, Product specific USP monograph

Drug product Stability

- A minimum of 3 submission batches
 - 12 M stability at CRT
 - 6 M stability under accelerated condition
 - 12 M stability under intermediate condition
- **Common deficiencies:**
 - X Insufficient stability duration to support 24 M expiry (ICH Q1E)

References: ICH Q1A, ICH Q1E

Drug product Stability

- X Lack of mass balance in stability data
 - (Assay vs. Total impurities, ICH Q1E)
- X Lack of justification/investigation for out of trend and out of specification results (ICH Q1E)
- X Lack of stability results for reconstitution of drug product per labeling
- X Lack of data to support stability of solid state at release and during shelf life

References: ICH Q1A, ICH Q1E, ICH Q6A



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Resources

1. USP General Chapter <2>
2. Harmonized Tripartite Guideline Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances ICH Q6A
3. FDA guidance for industry ANDAs: Impurities in Drug Products
4. Guidance for Industry Q3B (R2): Impurities in New Drug Products ICH Q3B
5. Establishing Impurity Acceptance Criteria as Part of Specifications for NDAs, ANDAs, and BLAs Based on Clinical Relevance. MaPP 5017.2
6. ICH Q1A: Guidance for Industry Q1A (R2): Stability Testing of New Drug Substances and Products
7. Guidance for Industry Photostability Testing of New Drug Substances and Products Q1B
8. Harmonized Tripartite Guideline Evaluation For Stability Data ICH Q1E

Question 1



The Drug Product (Q) is a narrow therapeutic product (NTI). The MDD is 2 mg and the Assay limit is 95% - 105%. In line with the recommendation of ICH Q3B, firm proposes the following limits for organic impurities:

- *Impurity Y (Specified Identified Degradation Product): NMT 1.0 %*
- *Impurity Z (Specified Identified Degradation Product): NMT 1.0 %*
- *Impurity at RRT X (Specified Unidentified Degradation Product): NMT 0.5 %*
- *Any Unspecified Degradation Product: NMT 0.5 %*

The overall acceptance criteria for organic impurities are acceptable

A: True

B: False

Question 2

Based on the ICH Q3B, firm proposes the following acceptance criteria for organic impurities in the drug product (NTI, MDD of 2 mg):

- *Impurity Y (Specified Identified Degradation Product): NMT 1.0 %*
- *Impurity Z (Specified Identified Degradation Product): NMT 1.0 %*
- *Impurity at RRT X (Specified Unidentified Degradation Product): NMT 0.5 %*
- *Any Unspecified Degradation Product: NMT 0.5 %*
- *Total Degradation product: NMT 3.5 %*

The limit for “Total Degradation Products” should be:

- A. NMT 3.5 %**
- B. NMT 3.0 %**
- C. NMT 2.5 %**
- D. NMT 2.0 %**



Thank you

Question?

