Impurity and Stability Studies

Definition of Impurities

Basic Idea

- An impurity is any component present in a drug substance or active pharmaceutical ingredient (API) that is not the intended chemical entity.
- Impurities may be formed during the manufacturing process, storage, packaging, or transportation of the drug.
- Impurities can affect the safety, efficacy, quality, and stability of pharmaceutical products.

Importance of Impurity Studies

- Impurity studies help ensure the quality and safety of medicines.
- Identification and control of impurities are essential for regulatory approval.
- Monitoring impurities helps maintain batch-to-batch consistency.
- Impurity profiling helps manufacturers improve production processes.

Sources of Impurities

1. **Raw Materials**
   - Impurities may be present in starting materials and reagents.
2. **Manufacturing Process**
   - Chemical reactions may produce unwanted by-products.
3. **Degradation During Storage**
   - Exposure to heat, light, moisture, or oxygen may generate degradation products.
4. **Packaging Materials**
   - Chemicals may migrate from containers or closures into the product.
5. **Environmental Contamination**
   - Impurities may enter the product from equipment, air, water, or handling processes.

Importance of Impurity Control

- Impurity control helps ensure patient safety.
- It maintains the quality and effectiveness of the drug.
- It supports regulatory approval.
- It ensures consistency between different manufacturing batches.

First Hope

Copyright by Engacy Learning Private Limited. All rights reserved. Reproduction or distribution without written consent is strictly prohibited.

Classification of Impurities in Drug Substance or Active Pharmaceutical Ingredients (APIs)

Basic Idea

- Impurities in drug substances are classified according to their source and nature.
- The International Council for Harmonisation (ICH) provides guidelines for the identification, qualification, and control of impurities.

Quality Requirements for API

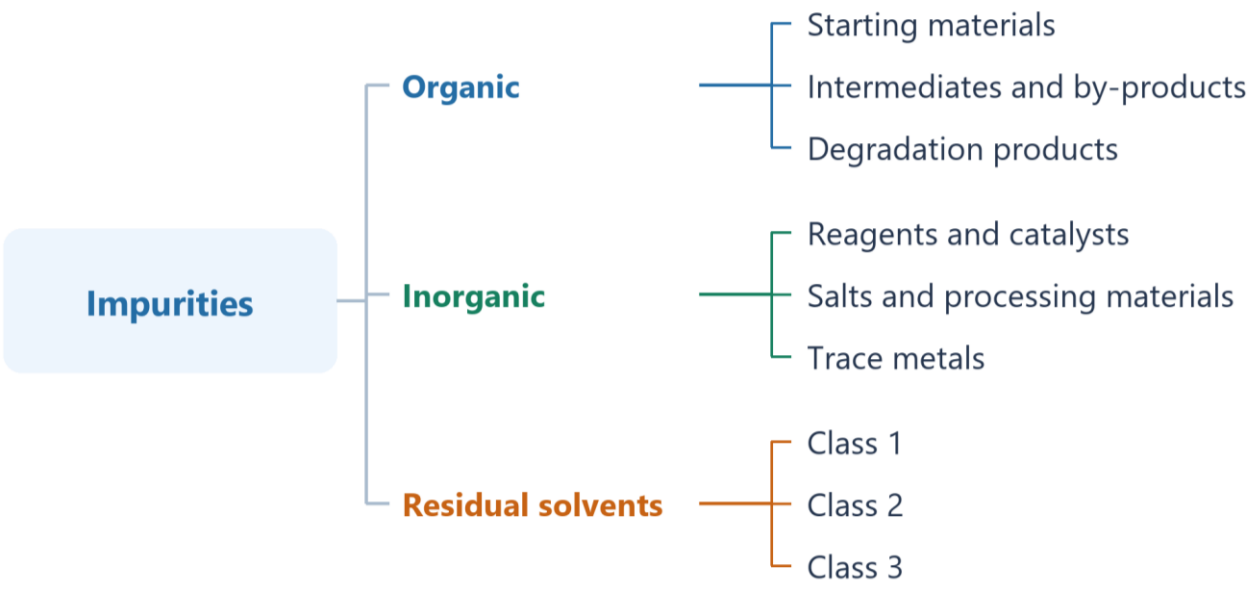
- The API should have a well-defined chemical structure.
- The API should contain impurities within acceptable limits.
- The API should remain stable throughout its intended shelf life.
- The API should comply with regulatory specifications.

Importance of Impurity Evaluation in APIs

- Impurities may alter the pharmacological activity of the API.
- Certain impurities may cause toxicity.
- Impurities may reduce the stability of the drug product.
- Proper impurity control ensures consistent therapeutic outcomes.

First Hope

Types of Impurities



Impurities are grouped by their chemical nature and their source.

1. Organic Impurities

- Organic impurities arise during the manufacturing process or storage of drug substances.
- These impurities may be identified or unidentified.

Copyright by Engacy Learning Private Limited. All rights reserved. Reproduction or distribution without written consent is strictly prohibited.

Sources of Organic Impurities

1. **Starting Materials**
   - Residual starting materials may remain in the final product.
2. **Intermediates**
   - Incomplete reactions may leave intermediate compounds.
3. **By-products**
   - Unwanted side reactions may generate by products.
4. **Degradation Products**
   - Drug substances may degrade during storage.
5. **Reagents, Catalysts, and Ligands**
   - Small amounts of processing chemicals may remain in the final product.

2. Inorganic Impurities

- Inorganic impurities usually originate from the manufacturing process.

Sources of Inorganic Impurities

1. **Reagents and Catalysts**
   - Residual metals and inorganic salts may remain after production.
2. **Filter Aids**
   - Materials used during purification may introduce impurities.
3. **Charcoal and Other Processing Materials**
   - Purification agents may contribute to impurities.
4. **Heavy Metals**
   - Trace amounts of metals may contaminate the product.

3. Residual Solvents

- Residual solvents are volatile organic chemicals used during manufacturing that remain in the final drug substance.
- These solvents should be removed as much as possible because they may pose health risks.

Classification of Residual Solvents According to ICH Q3C

1. Class 1 Solvents

- These solvents should be avoided because they are known human carcinogens or environmental hazards.
- Examples include benzene and carbon tetrachloride.

Copyright by Engacy Learning Private Limited. All rights reserved. Reproduction or distribution without written consent is strictly prohibited.

2. Class 2 Solvents

- These solvents should be limited because they have significant toxicity.
- Examples include methanol, acetonitrile, and toluene.

3. Class 3 Solvents

- These solvents have low toxic potential.
- Examples include ethanol, acetone, and acetic acid.

Quantification of Impurities as per ICH Guidelines

Basic Idea

- The ICH has established guidelines to determine when impurities should be reported, identified, and qualified.
- The limits depend on the maximum daily dose of the drug substance.
- ICH Q3A(R2) provides guidance for impurities in new drug substances.

Important Terms

First Hope

1. Reporting Threshold

- The reporting threshold is the level above which an impurity must be reported.

2. Identification Threshold

- The identification threshold is the level above which the chemical structure of an impurity should be identified.

3. Qualification Threshold

- The qualification threshold is the level above which the biological safety of an impurity should be established.



Reporting, identification and qualification address different regulatory questions; the applicable limits depend on the guideline and daily dose.

Threshold Limits for Drug Substances According to ICH Q3A(R2)

Copyright by Engacy Learning Private Limited. All rights reserved. Reproduction or distribution without written consent is strictly prohibited.

For Maximum Daily Dose Less Than or Equal to 2 g/day

Threshold Type	Limit
Reporting Threshold	0.05%
Identification Threshold	0.10% or 1.0 mg/day intake, whichever is lower
Qualification Threshold	0.15% or 1.0 mg/day intake, whichever is lower

For Maximum Daily Dose Greater Than 2 g/day

Threshold Type	Limit
Reporting Threshold	0.03%
Identification Threshold	0.05%
Qualification Threshold	0.05%

Methods Used for Quantification

1. Chromatographic Techniques

- High-performance liquid chromatography (HPLC) is commonly used.
- Gas chromatography (GC) is used for volatile impurities and residual solvents.

2. Spectroscopic Techniques

- Mass spectrometry (MS) helps identify unknown impurities.
- Nuclear magnetic resonance (NMR) spectroscopy helps determine chemical structures.

3. Elemental Analysis

- Inductively coupled plasma mass spectrometry (ICP-MS) is used to detect elemental impurities.

Requirements for Analytical Methods

- Methods should be specific and able to separate impurities from the API.
- Methods should be accurate and precise.
- Methods should be validated according to ICH guidelines.
- Methods should detect impurities at very low concentrations.

Importance

- Quantification helps ensure that impurity levels remain within acceptable limits.
- Proper impurity control improves patient safety.
- Regulatory compliance is achieved through adherence to ICH guidelines.

First Hope

Copyright by Engacy Learning Private Limited. All rights reserved. Reproduction or distribution without written consent is strictly prohibited.

First Hope

FREE PREVIEW

Click here to visit our website

PHARMACY PREMIUM NOTES

Complete subject and semesters are available on FirstHope app only.

Scan or click here

Click here to get the app >

Available on Google Play

JOIN THE FIRSTHOPE COMMUNITY

Join our Telegram channel

Click here to join Telegram >

Scan or click here

@FirstHopeNotes

Instagram

@firsthope.official

Click here to follow >

YouTube channel

FirstHope-Pharmacy / Live streams

Click here to watch >

WhatsApp channel

Follow FirstHope on WhatsApp

Click here to join >

FirstHope website

firsthope.co.in

Click here to visit >

B.Pharm / D.Pharm / M.Pharm / Pharm.D

Preview notes. Complete subjects and semesters in the FirstHope app.