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What is the difference between related compounds and related substances in pharmaceutical HPLC - FAQ

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In pharmaceutical analysis—particularly in HPLC (High-Performance Liquid Chromatography)—the terms related compounds and related substances are often used to describe impurities. While they are sometimes used interchangeably, they have distinct meanings in regulatory and analytical contexts.

Related Compounds

- Definition: Related compounds include all process-related substances that are chemically or structurally associated with the active pharmaceutical ingredient (API).
- These may include:
  - Synthetic intermediates
  - By-products
  - Degradation products formed during formulation or storage
- According to regulatory definitions, a related compound is any component of a drug substance that is not the defined chemical entity, and in the case of a drug product, not a formulation ingredient.

Examples of Related Compounds

1. **Starting Materials**
   - Residual raw materials used in the synthesis of the API.
   - Example: If the API is paracetamol, residual p-aminophenol (a precursor) may be a related compound.
2. **Synthetic Intermediates**
   - Compounds formed during intermediate steps of synthesis that may remain in trace amounts.
   - Example: In the synthesis of atorvastatin, intermediates like lactone derivatives may be present.
3. **Isomers**
   - Structural or stereoisomers of the API that may form during synthesis.
   - Example: Cis/trans isomers or enantiomers of a chiral drug.
4. **By-products**
   - Unintended compounds formed due to side reactions during synthesis.
   - Example: In the production of amlodipine, oxidized or hydrolyzed by-products may occur.
5. **Degradation Products**
   - Compounds formed when the API breaks down due to heat, light, pH, or oxidation.
   - Example: Aspirin can degrade into salicylic acid and acetic acid over time.
6. **Over-reacted or Under-reacted Species**
   - Compounds that result from incomplete or excessive reactions.

- Example: Excess alkylating agents or partially reacted intermediates.

These related compounds are typically monitored and controlled according to regulatory guidelines (e.g., ICH Q3A/B) to ensure the safety, efficacy, and stability of the pharmaceutical product [1].

References [1] Related Substances (RS) Calculation in HPLC

Related Substances

- Definition: Related substances are structurally related impurities that may arise from the manufacturing process, starting materials, or storage.
- These can be:
  - Identified or unidentified impurities from synthesis (e.g., starting materials, intermediates, by-products)
  - Degradation products formed during manufacturing or over time
- Related substances are often monitored as part of ICH guidelines (e.g., ICH Q3A/B) to ensure product safety and quality.

Examples of Related Substances

Related substances are typically **structurally related impurities** that may arise from the synthesis, manufacturing, or storage of a drug substance or product. These include:

1. **Unreacted Starting Materials**
   - Residual raw materials that were not fully consumed during synthesis.
   - *Example:* In the synthesis of an API, leftover benzyl chloride or other reagents.
2. **Synthetic Intermediates**
   - Compounds formed during intermediate steps that may remain in trace amounts.
   - *Example:* A partially reacted ester or amide intermediate.
3. **By-products**
   - Unintended compounds formed due to side reactions.
   - *Example:* Dimerization or rearrangement products during synthesis.
4. **Isomeric Impurities**
   - Structural or stereoisomers of the API that may form during synthesis.
   - *Example:* Cis/trans or enantiomeric forms of a chiral drug.
5. **Degradation Products**
   - Compounds formed due to chemical breakdown of the API during manufacturing or storage.
   - *Example:* Hydrolysis products of esters or oxidation products of phenols.
6. **Unknown Impurities**
   - Peaks observed in the chromatogram that do not correspond to known substances.
   - These are often monitored and controlled under ICH guidelines as “unidentified impurities.”

These substances are typically quantified and controlled using validated HPLC methods, and their levels must comply with regulatory thresholds to ensure **drug safety, efficacy, and stability** [1].

References [1] Related Substances (RS) Calculation in HPLC

USP Classification of Impurities

The United States Pharmacopeia (USP) classifies impurities into three main categories:

1. Organic Impurities – process-related or drug-related
2. Inorganic Impurities – residual metals, reagents, etc.
3. Residual Solvents – leftover solvents from synthesis

Why This Matters

- Understanding the distinction helps ensure regulatory compliance, accurate impurity profiling, and robust method development.
- Proper identification and quantification of both related compounds and related substances are critical for drug safety, efficacy, and stability.

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