The Complexity of Setting Specifications for Excipient Composition and Impurities

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Multiple stakeholders; one objective.
“The presence of any unlabeled other impurity in an official substance is a variance from the standard if the content is 0.1% or greater.

The sum of all other Impurities combined with the monograph-detected impurities may not exceed 2.0% unless otherwise stated in the monograph.”

This statement is not appropriate for excipients. If a distinction is not made between concomitant components and impurities......
What Is An Impurity?

**ICH:** Any component of the new drug product that is not the drug substance or an excipient in the drug product.¹

**FDA:** Any component of the new drug substance that is not the chemical entity defined in the new drug.²

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¹ ICH Harmonized Tripartite Guideline Impurities in New Drug Products Q3B (R2) 2006
² Guidance for Industry Q3A Impurities in New Drug Substances 2008
Why the Complexity?

- Most Excipients are **NOT** pure substances
- Other “components” present as an inherent part of excipient composition
What Impacts Excipient Composition?
Excipient Raw Material Sources & Implications
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- Mining operations (minerals)
  - Changes in location
    - Within a mining operation
    - A new or different mining operation
  - Changes in ore assay

- Agriculture...crops, livestock, forestry, oceans
  - Annual growing conditions
    - Weather
    - Soil
    - Temperature
  - Climate changes/shifts

- Petroleum
  - Drilling/extraction location
  - Purification/isolation methods

- Synthetics
  - Raw material sources and “what comes with them”
  - Residual/unreacted chemical/reactants
Other Effects & Consequences on Excipient Composition

- **Manufacturing processes**
  - Plant-to-plant differences
  - Manufacturer-to-manufacturer differences

- **Process capabilities**
  - Batch size
    - Kilos vs metric tonnes
  - Reproducibility
    - Lot-to-lot variation/excipient variability
    - Process controls/metrics

- Composition and performance relationships are not so well-defined
  - How do compositional changes impact performance?

- Polymorphs may be possible for some excipients
Example: Cellulose

- A single pulping mill can produce the global pharmaceutical industry’s annual cellulose requirement in a week
  - Includes all cellulose types
    - Powder
    - MCC
    - derivatized cellulosics/cellulose polymers
- Trees are not simply cellulose
  - $\alpha$-cellulose
  - Hemi cellulose
  - Resin
  - lignin
- Tree stock
  - Softwood vs hardwood
    - Can affect optimal DP
- Chip aging
  - Affects resin content
- Soil composition/weather may alter trace minerals
What Is An Impurity?

- **IPEC**: An undesirable material found in an excipient as a consequence of the raw materials, excipient manufacturing process, or excipient degradation.¹

- **FDA**: Any component of the new drug substance that is not the chemical entity defined in the new drug.²

¹ The International Pharmaceutical Excipient Council General Glossary of Terms and Acronyms, 2014.
² Guidance for Industry Q3A Impurities in New Drug Substances 2008
Substances found in excipients that:

- Are related to the intended chemical entity
- Likely necessary for assuring the proper excipient performance in its intended use.
- Are **NOT** impurities or **foreign substances**

- It is / they are natural to the excipient and its composition
Concomitant Components

**Concomitant Component** – “A substance found in an excipient that is not the intended chemical entity, may be necessary for assuring the proper performance of the excipient in its intended use, and is **not** an impurity or a foreign substance.” (Formerly referred to as minor component.)*

Excipient Composition

Excipient = \{ \text{Nominal or Labeled Ingredient} + \text{Concomitant Component(s)} + \text{Additives} + \text{Process Aids} + \text{Impurities} \} = 100\%
Setting Excipient Composition and Impurity Specifications is Complex

- Many excipients are not pure substances
  - Compositional variation may result

- Excipients are often naturally sourced
  - Seasonal and/or geographic changes can impact excipient composition and impurity profiles due to changes in raw materials

- Manufacturing processes can affect impurities levels
  - Changes in equipment and scale
    - Plant-to-plant and/or supplier-to-supplier

- Compositional changes can impact functional performance
  - Caution toward universally defined FRCs
Thank You...

Questions?