Multiple stakeholders; one objective.

The Complexity of Setting Specifications for Excipient Composition and Impurities

Joseph Zeleznik
Mgr of Technical & Regulatory Affairs
MEGGLE USA

IPEC-Americas QbD/EC Committee Chair
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.\(^2\)

\(^2\) ICH Harmonized Tripartite Guideline Impurities in New Drug Products Q3B (R2) 2006
Why the Complexity?

- Most Excipients are **not** pure substances
- Other “materials” present as an inherent part of an excipient
What Impacts Excipient Composition?
Excipient Raw Material Sources & Implications
Excipient Raw Material Sources & Implications

- **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
  - Reproducibility

- Composition and performance relationships are not so well-defined
  - How does a compositional change affect performance?

- No stability indicating assay exists for most excipients
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. ³

Excipient Composition: Other Components

- 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
Excipient Composition

\[
\text{Excipient} = \left\{ \text{Nominal or Labeled Ingredient} + \text{Concomitant Component(s)} + \text{Additives} + \text{Process Aids} + \text{Impurities} \right\} = 100\%
\]
Conclusion: Why the Complexity?

- Many excipients are not pure substances
- 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
- Compositional changes can impact functional performance