USP Open Forum | Excipients

USP Review of Stimuli Article's Proposed Definitions relating to Excipient Composition

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Focus on excipient composition

Single component

- Single source, excipients

  (Lactose, Nitric acid, Myristyl alcohol, Sodium Carbonate)

- Multisource, excipients (Sucrose)

Multiple component /mixtures

- Palm Kernal Oil (natural oils) , Mono-and di-glycerides
- Paraffin, Synthetic Paraffin, Sorbitan Monolaurate, Magnesium stearate

Mixtures of excipients that have been altered by processing

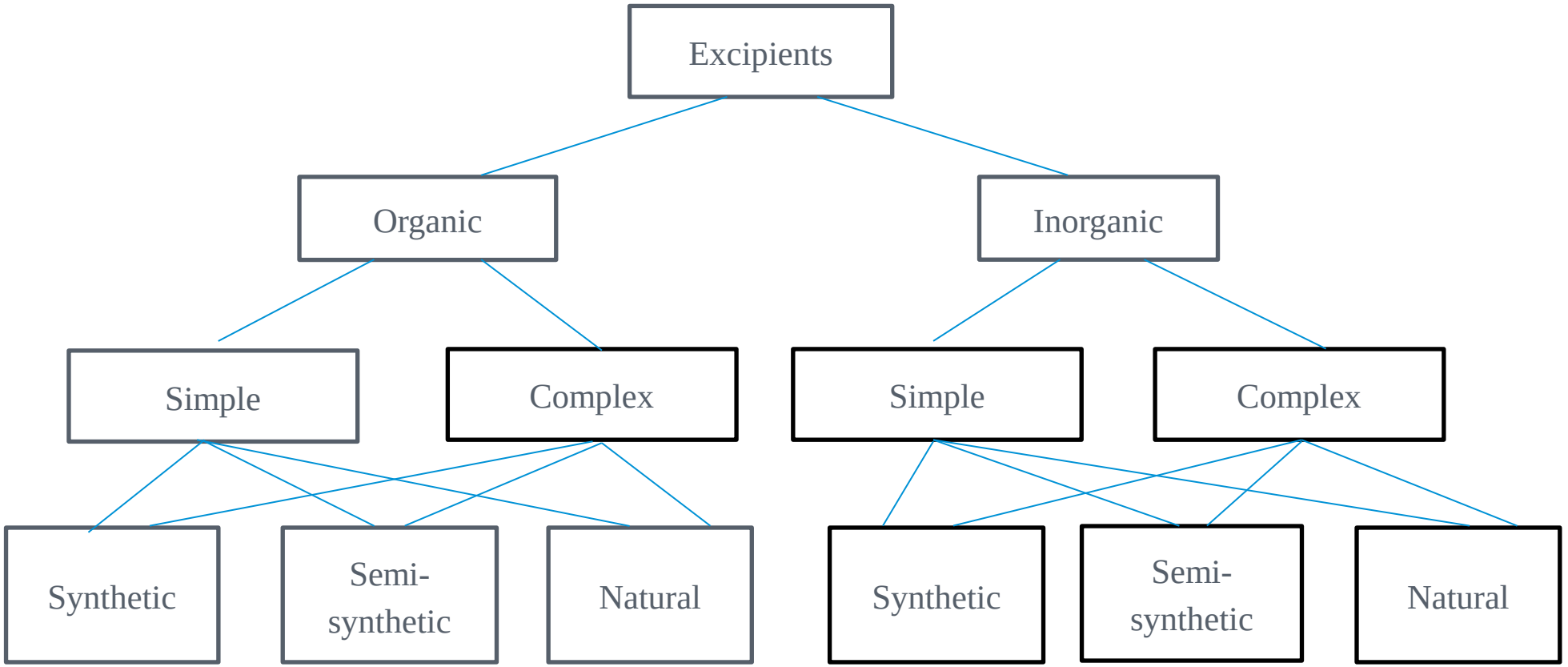
- Microcrystalline Cellulose and Carboxymethylcellulose Sodium

Complex (polymers, synthetic and natural, mixtures)

- Polyvinyl Alcohol, Polyethylene Glycol, Polydextrose, Polyisobutylene, Polyoxyl 40 stearate, Polyoxyl 20 cetostearyl ether

Focus on excipient composition

The *Stimuli* article classified excipients into the following substances:



Focus on excipient composition

- An excipient's composition can be defined as a set of components that comprise materials used as pharmaceutical excipients in drug products:
  - Nominal component
  - Concomitant component
  - Added substances
  - Residual starting materials, reagents, solvents, and catalysts
  - By–products
  - Intermediates
  - Degradation products

impurities

Stimuli article - classification of each substance as either an acceptable part of the excipient composition, or an impurity, is challenging.

Stakeholder engagement with proposed *Definitions*

- USP has been collaborating with and seeking input from manufacturers and users of excipients, FDA, external and internal laboratories, and academia:
  - The 2018 *Stimuli* article introduced the definitions for excipient components.
  - The 2018 survey collected stakeholder input and feedback on the definitions.
  - A summary of the *Stimuli* article and a link to the survey were shared at the October 2018 PNP Stakeholder Forum.
    - USP encouraged all stakeholders to read and comment on the article and to complete the survey.
  - A summary of the Stimuli article containing the definitions for excipient components was shared at Dec 2018 Excipient Stakeholder Forum.
  - The definitions for excipient components were discussed at Apr 2020 PNP Stakeholder Forum.
- The Open Forum will hopefully assist with providing further input on these proposed definitions. Input from all stakeholders is critical to the development of definitions.

Stakeholder engagement with proposed *Definitions*

- **Simple excipient:** An excipient composed of a single main substance with a well-defined chemical structure that can be characterized well analytically.
  - Case Study 2: Methyl Salicylate: classified as a simple excipient consisting of a well-characterized single nominal component of NLT 98.0% and NMT 102.0%.
  - Case Study 3: Deoxycholic Acid: classified as a simple excipient consisting of a single well-characterized nominal component of NLT 97.0% and NMT 103.0% .

Stakeholder engagement with proposed *Definitions* (cont.)

- **Complex excipient:** Any excipient that does not fit the definition of a simple excipient.
  - Case Study 4: Polyethylene Glycol 3350: classified as a complex excipient.
    - Polyethylene Glycol 3350 is defined as an addition polymer of ethylene oxide and water, represented by the formula $H(OCH_2CH_2)_nOH$, in which n represents the average number of oxyethylene groups. The apparent weight-average molecular weight is 3015–3685 g/mol (Da). It contains NLT 97.0% and NMT 103.0% of polyethylene glycol 3350, calculated on the anhydrous basis. It may contain a suitable antioxidant.
  - For polymeric and mixture type excipients, USP closely works with stakeholders to address composition, concomitant components, and/or impurities.

Stakeholder engagement with proposed *Definitions* (cont.)

- **Nominal component:** Substance typically found in the excipient that is expressed by the official name and definition and/or assay provided in the USP monograph.
  - Glycerin is classified as a simple excipient consisting of a well-characterized single nominal component.

DEFINITION
Glycerin contains NLT 99.0% and NMT 101.0% of $C_3H_8O_3$, calculated on the anhydrous basis.

  - Glyceryl Dibehenate is classified as a complex excipient, a mixture of diglycerides, mainly glyceryl dibehenate.

DEFINITION
Glyceryl Dibehenate is a mixture of diglycerides, mainly glyceryl dibehenate, together with variable quantities of monoglycerides and triglycerides. It contains NLT 15.0% and NMT 23.0% of monoglycerides, NLT 40.0% and NMT 60.0% of diglycerides, and NLT 21.0% and NMT 35.0% of triglycerides. It is obtained by esterification of glycerin with behenic (docosanoic) acid. The fatty acid may be of vegetable or synthetic origin.

Stakeholder engagement with proposed *Definitions* (cont.)

- **Minor component:** A component of an excipient which is not the nominal component or, where the official name does not relate to the excipient components, not the major component.
  - Minor components are often not specified at all, or they may be specified with upper limits for reasons that should not lead as a rule to their classification as impurities. It is important to remember that these minor components probably have always been in the excipient.
  - All minor components are initially looked at as potential impurities unless it can be otherwise justified. In the case of simple excipients, when minor components exceed 0.1%, the Expert Committees' general approach is to identify what those components are, if possible.

Stakeholder engagement with proposed *Definitions* (cont.)

- **Minor component:**
  - *Stimuli* article example: Oleyl Alcohol:
    - One group of the drug manufacturers preferred Oleyl Alcohol with the content of oleyl alcohol within 78%–85% and minor components within 15% –22%. They reported that those minor components were necessary and useful for their topical drug formulations.
    - In contrast, the other group preferred Oleyl Alcohol of greater than 95% purity with limited amounts of minor components because those components negatively impacted their specific formulations.

Stakeholder engagement with proposed *Definitions* (cont.)

- **Concomitant component:** A minor component of an excipient that accompanies the nominal component which is identified either in the title or definition of a monograph. Concomitant components are characteristic of many excipients and are not considered to be impurities if there is no negative impact on drug products. Some but not all concomitant components are defined or specified in excipient monographs. Added substances are not considered concomitant components. (Any component that can be considered a toxic impurity because of significant undesirable biological effect is not considered to be a concomitant component.)

Glyceryl Dibehenate

DEFINITION

Glyceryl Dibehenate is a mixture of diglycerides, mainly glyceryl dibehenate, together with variable quantities of monoglycerides and triglycerides. It contains NLT 15.0% and NMT 23.0% of monoglycerides, NLT 40.0% and NMT 60.0% of diglycerides, and NLT 21.0% and NMT 35.0% of triglycerides. It is obtained by esterification of glycerin with behenic (docosanoic) acid. The fatty acid may be of vegetable or synthetic origin.

Stakeholder engagement with proposed *Definitions* (cont.)

- **Concomitant component:**
  - The term “concomitant component” is used in this *Stimuli* article to encompass all components that are a necessary part of the excipient, and hence should not be considered impurities unless they are shown in some way to compromise the quality of the excipient.
  - May have a beneficial effect in the use of the excipient.
  - Many of the components present in excipients may be necessary for performance in different application and are thus not impurities but concomitant components.
    - Magnesium Stearate:
      - Nominal component: Magnesium Stearate.
      - Minor component: magnesium palmitate usually found with Magnesium Stearate (synergistic lubrication effect)

Stakeholder engagement with proposed *Definitions* (cont.)

- **Concomitant component:**
  - Concomitant components are often not part of the excipient specification, although for some, a limit might be specified. These limits often result from what is learned about the excipient composition when testing commercially available samples of excipients.
  - Concomitant components might be detected in analyses such as chromatographic assays designed to measure the major and perhaps other known minor components of the excipient for which limits are specified in the official method.
  - Often, it is difficult to make an unambiguous determination whether such a component is a concomitant component, or an impurity (e.g., the presence of hemicelluloses in microcrystalline cellulose or other polyhydric alcohols and any hexitol anhydrides in Sorbitol).

Stakeholder engagement with proposed *Definitions* (cont.)

- **Added substances in official substances:** Substances added to improve excipient handling, processing or performance, including stability (see also General Notices, 5.20.10 Added Substances in Official Substances).
  - Although, the Excipient Impurities Joint Subcommittee recognizes the importance of Added Substances in the excipient's composition, this topic will be discussed as part of the next steps (formation of a Project Team).

Stakeholder engagement with proposed *Definitions* (cont.)

- **Excipient impurity:** Any substance that detracts from the quality of the excipient (i.e., that is not the substance appearing in the official name, or a concomitant component or added substance as defined.)
  - The term “impurity” or “impurities” has a negative connotation and may not be appropriate for excipients when no negative impact is associated with the presence of a minor component, especially if the minor component has a favorable impact or is necessary for the excipient to perform correctly in a drug product.
  - The performance of an excipient does not always correlate with purity.

Addressing excipient components in monographs

Some examples:

Propylene Glycol Dicaprylate/Dicaprate

DEFINITION

Propylene Glycol Dicaprylate/Dicaprate is a mixture of the propylene glycol mono- and diesters of caprylic acid ($C_8H_{16}O_2$) and capric acid ($C_{10}H_{20}O_2$), the diesters fraction being predominant.

Specific Tests

• **FATS AND FIXED OILS, *FATTY ACID COMPOSITION* (401)**: Propylene Glycol Dicaprylate/Dicaprate exhibits the composition profile of fatty acids shown in the following table:

Carbon-Chain Length	Number of Double Bonds	Percentage (%)
6	0	≤2.0
8	0	50.0–80.0
10	0	20.0–50.0
12	0	≤3.0
14	0	≤1.0

Polyglyceryl 3 Diisostearate

DEFINITION

Polyglyceryl 3 Diisostearate is a mixture of polyglyceryl diesters of mainly isostearic acid, obtained by esterification of polyglycerin and isostearic acid. The polyglycerin consists mainly of triglycerin

ASSAY

• **CONTENT OF FATTY ACIDS**

Acceptance criteria

Sum of the contents of the fatty acids eluting between palmitic acid and stearic acid (excluding palmitic acid and stearic acid): NLT 60.0%

Sum of the contents of myristic acid, palmitic acid, and stearic acid: NMT 11.0%

Stakeholder engagement and feedback is critical!

- **The Excipient Impurities Joint Subcommittee is considering development of a general information chapter that would provide general principles, approaches, and guidelines on setting specifications for excipient composition and impurities.**
  - A glossary of definitions is considered as a helpful inclusion.
- The Joint subcommittee is seeking input from manufacturers and users of excipients.
- Input from all stakeholders is critical to the development of composition and impurity specifications.
- All interested parties are encouraged to comment on the views and approaches presented by the Excipient Impurities Joint Subcommittee in the *Stimuli article* during this **Open Forum**.

Thank You

Stay Connected

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