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The Real Complexity of Excipient Composition

This article seeks to promote dialogue among stakeholders to facilitate consensus regarding requirements for excipients.

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Since the *United States Pharmacopeia* (*USP*) and *National Formulary* (*NF*) General Notices combined, it could be interpreted that API requirements apply to excipients. In *USP–NF* General Notices, an API equals the labeled entity plus impurities. Applying this logic to excipients, anything NOT the labeled entity would be an "impurity." Most excipients are more complex and less well defined than APIs. The excipient name may not reflect its complete composition. The named entity may be a minor component. The other components may be essential for functionality. This article seeks to promote dialogue among stakeholders to facilitate consensus regarding this topic.

Due to excipient diversity, including highly complex mixtures from animal, botanical, mineral, and/or synthetic sources, differing approaches to characterizing excipient properties may be required. More complex excipients, including excipients produced by biotechnological methods, may require extensive physico-chemical characterization to fully understand their composition.

Excipients are a diverse group of materials, which are used for a vast range of available drug products. Excipients intended for use by different routes of administration may require different understanding of the composition profile. Excipient manufacturers should seek to establish how their ingredients will be used. However, in commerce, this information is not always available from or shared by the user.

IPEC-Americas and IPEC Europe have published an *Excipient Composition Guide*, which describes the complex nature of excipients (1). There are many excipient types, which have different compositional profiles. These include standard excipients, sometimes referred to as conventional or traditional excipients, mixed excipients, and co-processed excipients.

The excipient composition profile may be defined as a description of the components present in a typical excipient lot produced by a given manufacturing process. The main components of an excipient are those, which in most cases; contribute to the excipient being able to perform its intended function within the drug product(s) in which it is used (also known as "nominal" components). Other necessary components also may be present (i.e., concomitant components, additives, and processing aids). Unreacted starting materials, by-products, degradants, and residual solvents also may be present as a direct result of the excipient's manufacturing process. These components may arise at different stages in excipient processing (**Table I**) and are considered part of the excipient composition profile.

Table I: Differences in APIs and excipients.

Typical attributes	API (traditional, small molecules)	Excipient
End users	• Pharmaceutical companies • Cosmetic companies	• Industrial • Cosmetic • Food • Pharmaceutical (often only a small proportion of the market)
Manufacturing	• Batch (usually) • Small volume (usually < 1000 kg)	• Batch or continuous • Large volume (up to 100,000 tons per annum)
Synthesis	• Synthesis of specific molecular entity	• Synthesis (including polymerization) of predominant molecular entity • Extraction, processing, and/or purification of naturally-occurring starting materials
Raw materials	• Well-defined chemical intermediates	• Harvested plant matter • Animal products • Minerals (mined) • Fermentation
Composition	• Typical processing reduces or eliminates most impurities. • API = labeled entity + impurities = 100% • Quantitative assay	• Typical API purification techniques (e.g., crystallization, precipitation) are not applicable • Excipient = nominal labeled entity + concomitant components + additives + residual processing aids + impurities = 100% • Variable compositional profile, depending on source/process • Assay may not be available

Table I: Differences in APIs and excipients.

Finally, contaminants may be present (i.e., substances not directly resulting from the excipient manufacturing process [synthesis and/or purification], but as a consequence of extraneous factors such as personnel, equipment, packaging, other products, etc.). Contaminants would not be regarded as part of the composition profile; however, they should be controlled through good manufacturing practices (GMPs).

As excipients are used typically without further purification, excipient manufacturers should identify and set appropriate limits for components as appropriate. These limits should be based on appropriate safety data, limits described in official compendia, or other requirements and sound GMP considerations. Manufacturing processes should be adequately controlled to ensure that undesirable components do not exceed established limits.

For many excipients, classifying and quantifying all components may not be possible. Composition-related methods and specifications should be justified. There are many traditional, well-established (qualified by use) excipients for which it is neither feasible, nor necessary, for safety purposes to identify all components. Evaluating (re-evaluating) their safety, unless scientific evidence becomes available that suggests otherwise, is generally unnecessary. Where feasible, generating composition profiles should involve each component's identification, classification, and quantification

(expressed as a range). If unidentified, an appropriate qualitative description such as a chromatographic peak retention time should be made available. A reasonable reporting threshold is available from the International Council for Harmonization (ICH) Q3A (R2) guideline (2).

In addition to the “nominal” component, excipient components may comprise the following:

- Concomitant components
- Additives
- Processing aids
- Degradants
- Residual solvents

Additional components may comprise:

- Unreacted starting materials such as monomers in polymerization
- Residual catalysts or metal reagents
- Reaction by-products (e.g., isomers and side reactions)
- Raw material components (especially for naturally sourced materials).

Establishing an excipient composition profile

Where possible, excipient manufacturers should establish composition profiles where the main excipient components are identified and their normal concentration variability determined. Acceptable limits, where required, should be based on a risk assessment using sound science. It is typically not necessary to have limits for all components in the composition profile, but the profile should be understood. Limits should only be established when justified by risk assessment to address safety and/or customer-specific concerns.

An excipient composition profile evaluation should be performed by the excipient manufacturer using their manufacturing process knowledge and understanding, which may lead to identifying associated potentially undesirable components. Excipient components (i.e., main/concomitant components, additives, processing aids, and undesirable components) should be identified and quantified using suitable analytical techniques, wherever possible. Appropriate analytical methods may be compendial or suitably qualified manufacturer-specific methods. The materials used for composition profile development should be representative of the excipient, and sampled in a manner consistent with that used for lot release by the quality control unit (i.e., same sampling technique and sampling point(s) in the manufacturing process).

Concerns with current USP policies

The United States Pharmacopeial Convention (USP) merged the General Notices for both the
United States Pharmacopeia (*USP*) and *National Formulary* (*NF*) in early 2000. In effect, this means that the same General Notices restrictions apply to both APIs and excipients. It could, therefore, be argued that API requirements also apply to excipients. In the General Notices, an API equals the labeled entity plus impurities. If the same logic is applied to excipients, anything other than the labeled entity could be considered an "impurity."

The current *USP 40–NF 35* "impurity" or "concomitant component" definitions only apply to drug substances and drug products but not excipients. Similarly, ICH addresses impurities in new drug substances and drug products as follows:

> Any component of the new drug substance that is not the chemical entity defined as the new drug substance (2)
> Any component of the new drug product that is not the drug substance or an excipient in the drug product (3)
> Any component present in the intermediate or API that is not the desired entity (4).

These definitions do not specifically apply to excipients and cause confusion when inappropriately applied to them. Excipient-specific definitions are therefore required and should be included in future issues of the *USP–NF*.

The situation regarding excipients is put forth in an excerpt from the International Pharmaceutical Excipients Council (IPEC) Composition Guide:
"For excipients, the situation is more complex as they are frequently multicomponent, and their composition may be less well defined. Their functionality may be dependent on the presence of components other than the labeled entity. The definition of the term 'impurity' as used above for drug product and/or drug substance is thus misleading when applied to excipients. To distinguish these components from true impurities, the appropriate term for describing excipients should be 'minor component' or 'concomitant component' (e.g., the water of crystallization in magnesium stearate required for optimum lubricant effectiveness)" (1).

Advances in analytical technologies can give excipient manufacturers, users, and regulators more quantitative excipient composition detail, but not necessarily increased understanding of excipient functionality. Increased analytical capabilities are to be encouraged, but, taken out of context, can cause confusion and inappropriate or counterproductive actions by users and regulators.

Significant differences between APIs and excipients

FDA defines an "Active Ingredient" (here used interchangeably with the term API) as "any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals" (5). FDA does not have an official definition for "excipient," but rather uses the term "Inactive Ingredient," which they define as "any component of a drug product other than the active ingredient" (6).

The Glossary found in *USP 40–NF 35* General Chapter <1078> Good Manufacturing Practices For Bulk Pharmaceutical Excipients defines an excipient as "Any substance, other than the active pharmaceutical ingredient or drug product, that has been appropriately evaluated for safety and is included in a drug delivery system to aid the processing of the drug delivery system during manufacture; to protect, support, or enhance stability, bioavailability, or patient acceptability; to assist in product identification; or to enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use" (7).

Some of the general differences between APIs and excipients are summarized (**Table I**). Exceptions exist (e.g., in the case of small-molecule synthetic API-like excipients and naturally derived APIs such as digitalis and fish oil).

In the case of APIs, the labeled entity is generally well-defined and quantified by assay to ensure purity. Other components are considered impurities, that is, the balance of 100% minus the assay. For excipients, the labeled entity can be nominal, and there is not always a specific assay (e.g., microcrystalline cellulose). The labeled entity itself may not even be the predominant component. For example, stearic acid 50 NF can contain as little as 40 wt. % stearic (octadecanoic) acid and as much as 50 wt. % palmitic (hexadecanoic) acid. The latter major component is a concomitant component, not an impurity. There may also be up to 10 wt. % other components. The labeled entity may also be nominal for polymeric excipients, usually reflecting an average molecular weight.

According to General Notices 5.60.10 in *USP 40–NF 35*, "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" (8).

This statement is not appropriate for excipients. If a distinction is not made between concomitant components, additives, residual processing aids, and impurities, there is likely to be confusion regarding excipient applicability of specific impurity identification and quantification requirements typical for APIs. This could encourage attempts to set inappropriate specifications by users and result in excipient shortages, if the specifications are outside the process capability of excipient manufacturers.

The authors propose that the following excipient-specific definitions be adopted by *USP–NF*:

> 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) (9)
> Additives—A substance added to the excipient to improve or maintain a characteristic such as a preservative, flow agent, antimicrobial, etc. (9)
> Processing aids—A material added to a manufacturing step for the purpose of facilitating the completion of that step or subsequent step (9)
> Impurity—An undesirable material found in an excipient as a consequence of the raw materials, excipient manufacturing process, or excipient degradation (9).

Excipient composition example-Polyethylene Glycol 600

Excipients can be complex mixtures of substances, some or all of which may affect functionality. Polyethylene glycol 600 NF (PEG 600), which is a complex mixture of the tridecamer (mol. wt. 590), other oligomers (concomitant components), and impurities, is a good example. It is by no means the only example. Other examples include polymeric excipients, some excipients derived from natural fats and oils, and mineral ores.

Polyethylene glycols are polymers of ethylene oxide and water. In the NF, the number after polyethylene glycol or PEG indicates the mean molecular weight of the polymer. PEG 600, which has been safely used as an excipient for many years, is used (among other applications) in hard and soft gelatin capsule formulations to enhance active substance solubility (10).

While the "600" nomenclature indicates mean molecular weight, other higher and lower molecular weight oligomers present impact performance. In addition, the specified impurities ethylene glycol and diethylene glycol must not jointly exceed 0.25 wt. %. A suitable antioxidant (additive) may also be present. The antioxidant would be a stabilizer and thus an additive, not an impurity.

Historically, polyethylene glycol grades were specified by viscosity, but their multicomponent nature is now revealed by modern chromatographic techniques. The Cleaver chromatogram (11) shows multiple oligomers present, most of which are present at levels well in excess of 0.1 wt. %, and the sum of which exceed 2 wt. %. Given the current impurity limits and "definition" put forth in the *USP–NF* General Notices, these oligomers could be construed as "impurities."
However, since finished pharmaceutical formulations using PEG 600 have been based on PEG 600 functionality, which is predicated on the presence of the oligomers shown in the chromatogram, the effect of removing all oligomers except the tridecamer is unknown, even if it were possible to do so. The presence of these oligomers may provide essential contribution to PEG 600 drug delivery properties. In addition, their presence does not pose a health or safety risk.

In the case of ethylene glycol and diethylene glycol, both of which could be present in PEGs, there is a clear need to set limits for the "undesirable substances" (impurities) because they are toxic to humans and animals.

Communication disclosure methods needed for additives and processing aids

IPEC-Americas recognizes the need to provide appropriate details regarding excipient composition. There are excipients in approved medicines, which contain undeclared additives or residual processing aids and yet have a long history of use. Given the large number of excipients involved, and the much greater number of pharmaceutical products potentially affected, there is a need for IPEC-Americas, FDA, and USP to collaborate in developing a path forward and avoiding potential drug product shortages. There has not been a consistent approach to excipient additives and residual processing aids disclosure, even though these ingredients have been used safely for many years. However, it must also be recognized that the presence of certain other components in excipients may present intellectual property issues (trade secrets and know-how). A mechanism is required, and should be developed, for sharing confidential information with FDA and without direct disclosure of the identity and level of additive or residual processing aids to users.

For an excipient having a monograph in the *USP–NF*, there are issues with such additives and residual processing aids. USP General Notices 5.20 Added Substances (12) states as follows:

"5.20. Added Substances

"Added substances are presumed to be unsuitable for inclusion in an official article and therefore prohibited, if: (1) they exceed the minimum quantity required for providing their intended effect; (2) their presence impairs the bioavailability, therapeutic efficacy, or safety of the official article; or (3) they interfere with the assays and tests prescribed for determining compliance with the compendial standards.

"The air in a container of an official article may, where appropriate, be evacuated or be replaced by carbon dioxide, helium, argon, or nitrogen, or by a mixture of these gases. The use of such gas need not be declared in the labeling.

"5.20.10. Added Substances in Official Substances

"Official substances may contain only the specific added substances that are permitted by the individual monograph. Such added substances shall not exceed the quantity required for providing their intended effect. Where such addition is permitted, the label shall indicate the name(s) and amount(s) of any added substance(s)."

The presence of undeclared additives and processing aids conflicts with General Notices requirements. A mechanism is needed for confidential disclosure of the presence of additives and residual processing aids without required labeling as specified currently by *USP–NF*.

IPEC-Americas has submitted a background document on this issue to FDA and has requested a meeting to discuss possible disclosure mechanisms for these ingredients and potential changes needed in the *USP–NF* General Notices.

Conclusion

Many excipients are multi-component with well-established safety profiles. Components other than the labeled entity may also impact excipient performance. For excipients, concomitant components, additives, and residual processing aids should be distinguished from impurities in terms of undesirable substances, which should be absent or controlled for safety reasons.

The current API-specific requirements put forth in the USP 40-NF 35 General Notices are not appropriate for excipients. It is therefore recommended that USP and FDA take the following actions:

- Revise General Notices 5.60.10 and 5.20.10 to address excipient requirements by incorporating the aforementioned proposed definitions.
- Include excipients in the list of exceptions in the Other Impurities requirements in 5.60.10.
- Provide excipient manufacturers with a means to confidentially communicate additives and residual processing aids presence to regulators without public disclosure.

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