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The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities[a]

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ABSTRACT

Setting specifications for excipients is complex due to the vast array of materials that are utilized in drug product formulation and is becoming increasingly more complicated with the need to update excipient monographs through the introduction of modern analytical techniques. These techniques provide additional information about the makeup of the excipients and a further understanding of the complexity of the materials utilized in the formulations of drug products. The variety of sources, manufacturing methods, and functionality of excipients must be considered when setting specifications. Strict adherence to guidelines intended for active ingredients when setting specifications for excipients is not always possible, advantageous, or necessary to ensure public safety. It is important to recognize the potential impact of excipients on product formulations and understand that any changes to the excipient specifications could have unintended consequences on effectiveness of drug products or impact the availability of materials needed to manufacture products. The February 2017 FDA–USP Workshop on the *Critical Importance of Excipients in Product Development—Why Excipients are Important Now and In the Future* highlighted the importance of advancing the science of excipient selection and regulatory evaluation that impact generic drug development (*1*). The workshop sought constructive input from a wide range of stakeholders and regulatory agencies in establishing a quality NF specification through up-to-date and harmonization initiatives.

This article will discuss the need to provide clear guidelines for setting specifications for excipients, to provide consistent practice, and to reduce the time it takes to gather information and set these specifications. It includes a discussion of the existing International Council for Harmonisation (ICH) Q3A (*2*) guidelines and USP *General Notices and Requirements* and the difficulties in applying these guidelines to excipients, as well as a discussion of the types of components and impurities that are found in excipients. Terminology and definitions are also provided.

INTRODUCTION

This Stimuli article is intended to 1) provide the views of the Excipient Impurities Joint Subcommittee on the complexity of excipient composition; 2) introduce definitions for simple excipient, complex excipient, excipient composition, and excipient impurity; and 3) describe challenges that the Excipient Monographs 1 and 2 (EM1 and EM2) Expert Committees (ECs) face in setting specifications for different components and impurities in excipients, and to provide a proposed direction and guidance in standards setting and establishing specifications for excipient components and impurities. Compared to drug substances, excipients often exhibit complex composition. An excipient composition can be defined as a set of components comprising the material used as a pharmaceutical excipient in drug products. The following is a list of components that could be in an excipient, and which are discussed in greater detail later:

- Nominal component
- Concomitant component
- Added substances
- Residual starting materials, reagents, solvents, and catalysts
- By–products
- Intermediates
- Degradation products

Classification of each substance as either an acceptable part of the excipient composition, or an impurity, is challenging. USP excipient monographs are being updated to improve methods for assessment of purity and identity. Similarly, in the development of new excipient monographs, USP seeks to include tests that will reveal excipient composition. This additional information can be advantageous, providing insights into how and why the composition may vary, for example, revealing how a change or differences in the manufacturing process for an excipient can impact excipient composition. However, we should not be overly constrictive in specifying composition. Setting appropriate specifications must balance between a desire to account for both the composition and impurities and practical limitations and the needs pertaining to excipient and drug product quality. To achieve this very challenging goal, USP collaborates with and seeks input from its stakeholders (including manufacturers and users of excipients, FDA, external and internal laboratories, and academia).

Many excipients are polymers or of plant, mineral, or animal origin. Thus, it remains challenging, or even impractical, to develop a specific assay which can accurately measure the percentage of each component. Often adding to the challenge of

developing an appropriate excipient specification is the lack of knowledge correlating excipient composition with the performance of the excipient in a particular drug product.

As USP makes progress in working towards "Resolution 2: *USP–NF* Monograph Modernization", adopted by the USP Convention Membership on April 25, 2015, more excipient monographs are being updated to include modern technologies that can help reveal excipient composition. In contrast to drug substances and drug products, there are no general chapters in *USP–NF* that provide guidance on how to specify excipient composition, including control of impurities. Substances present in excipients which are deliberately added are addressed in USP *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 at a later date. Two sections of *General Notices* (*5.60.10 Other Impurities in USP and NF Articles* and *5.60.20 Residual Solvents in USP and NF Articles*) cover impurities in official substances. However, as written, the applicability of these guidelines on impurities to excipients is questionable.

Furthermore, 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. Additionally, the performance of an excipient does not always correlate with purity.

The Excipient Impurities Joint Subcommittee is considering development of a general information chapter that would provide guidance on setting specifications for excipient composition and impurities. The subcommittee is seeking input from the manufacturers and users of excipients. Input from all stakeholders is critical to the development of composition and impurity specifications. Therefore, all interested parties are encouraged to comment on the views and approaches presented by the Excipient Impurities Joint Subcommittee in this *Stimuli* article.

To facilitate this, a survey will be launched concurrent with this *PF* publication to obtain feedback and comments from stakeholders regarding the idea of developing a general chapter on excipient composition and impurities in excipients. Specific survey objectives are to:

1. Identify overall needs and challenges regarding the current written standards (monographs and *General Notices*) on impurities in excipients
2. Assess the level of satisfaction with the current written standards on impurities for excipients
3. Identify opportunities for improvement
4. Analyze input on modernizing documentary standards on impurities in excipients
5. Determine potential challenges in implementing the new approach.

BACKROUND

The Federal Food, Drug and Cosmetic Act (FD&C Act) of 1938 defines the term "drug" to include components (i.e., the active ingredients and excipients) that go into the manufacture of finished drug formulations.

More recently, the ICH Q3A (*2*) Guidance (Impurities in New Drug Substances) was issued to provide "guidance for registration applications on the content and qualification of impurities in new drug substances." Note that ICH Q3A applies to drug substances and ICH Q3B applies to drug products, but neither applies to excipients. However, the ICH Q3 documents are a logical starting point for developing specifications for impurities in excipients, but there are some important limitations as discussed below.

The first consideration is how to treat components above thresholds which, for drug substances, would dictate that these be considered impurities and must be identified and/or specified and controlled. Such an approach to excipients from an excipient safety and functionality standpoint is thought to be either unnecessary or impractical. This is because many excipients are derived from natural sources or are, as defined and specified, relatively inhomogeneous in composition, and contain homologous components in minor amounts (e.g., Oleyl Alcohol NF can contain up to 8.0% of cetyl alcohol, 5.0% of stearyl alcohol, 7.0% of linoleyl alcohol, 1.0% of linolenyl alcohol, and up to 1.0% of arachidyl alcohol). Many of today's excipients have been used for many years and are composed of minor and variable amounts of substances which, absent any evidence of adverse impact, ought not to be considered impurities but rather part of the excipient. Minor amounts of components present due to natural derivation or by virtue of the manufacturing process may contribute to the excipient's functionality—and yet the function and identity of these components is often unknown. To add to the complexity, these other components may interact with each other or the main component in the excipient to give the excipient its specific functionality. However, in many cases these specific interactions and mechanisms that contribute to the excipient's overall functionality are not well understood.

Recently, the ability to detect adulterants in excipients has been questioned by stakeholders and regulators amid notable adulteration incidents that involved substitution or dilution and falsification of ingredient labeling. In response to these concerns, upon review of excipient monographs, it became apparent that nonspecific identification tests or assays which could not differentiate between the genuine article and one that contained even an appreciable, perhaps harmful, amount of an added adulterant, were a factor. FDA requested the identification and assay tests specified in pharmacopeial monographs for certain articles at greatest risk of intentional adulteration be improved or replaced with more specific tests to combat fraudulent activity

in the global supply chain. In response, USP initiated an excipient monograph modernization program (currently known as the USP Up-to-Date Initiative) which would incorporate up-to-date analytical techniques and mitigate adulteration risk.

One area related to the discussion on specification of impurities in excipients is the questionable applicability of *General Notices, 5.60.10 Other Impurities in USP and NF Articles* to excipients stating "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." This provision is intended to ensure that impurities found in drug substances are declared as impurities in the labeling. Applying the rules established by *5.60.10*, a substance present in a minor amount in an excipient and not specified or reported as part of the excipient assay could be regarded as an impurity. While *5.60.10* might apply to simple excipients (e.g., sodium hydroxide, mandelic acid), applying the rules would be problematic for excipients of natural origin, polymeric excipients, or excipients that usually contain larger amounts (>0.1%) of components related to the main or nominal component.

As with exceptions provided in *5.60.10* for complex drug substances, the reporting of minor components in excipients as "impurities not specified in the monograph" is not beneficial and may be counterproductive to drug product quality or availability. Therefore, reporting of each identified minor component in excipients of natural origin may not be possible at this time. One possible way to reconcile the differences with excipients and *5.60.10* is to add excipients to the exclusion list except in cases when the excipient application dictates the excipient be of high purity (e.g., dextrose used in parenteral formulations) and/or when an excipient is used as a drug substance (e.g., Polyethylene Glycol 3350).

An important driver for publishing this *Stimuli* article is a need to provide clearer direction and guidance to USP expert volunteers, scientists, and staff engaged in standards setting and establishing specifications for excipient components and impurities, including the use of representative samples to account for multiple manufacturing processes by which an excipient can be produced. This is especially true in cases where USP has no sponsor commitment.

Figure 1 illustrates classes of substances that can be used as excipients.

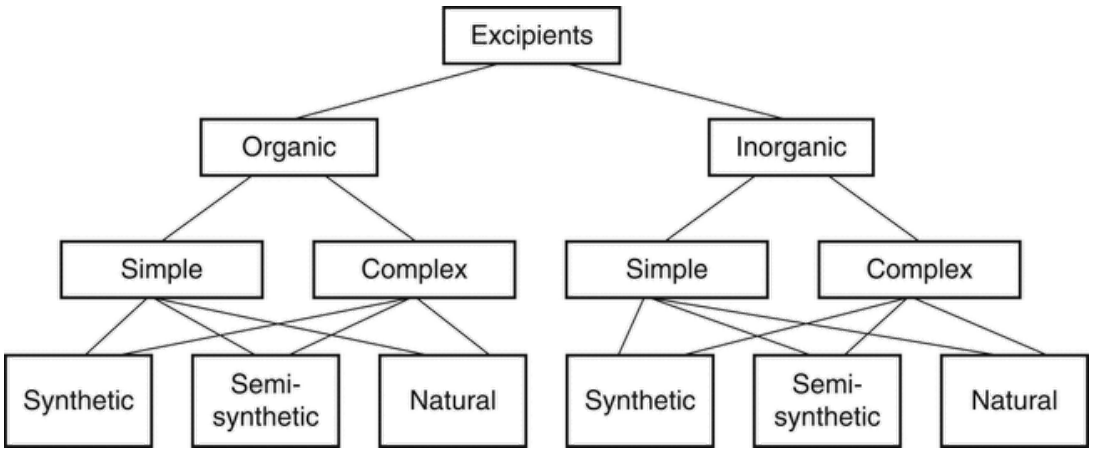


Figure 1. Classes of substances used as excipients.

The following information is provided to serve as examples of the types of difficulties encountered when setting specifications for excipients:

1. Biopolymers from natural materials and polymers synthesized from monomeric units:
    a. Variable lengths of polymer chains as well as how the chains are linked often account for functionality, in which case the isoforms with short-range chemical similarities clearly are not impurities and are more likely concomitant components.
    b. Components that are co-extracted in upstream processing of the excipient are less readily classified as impurities, even when their chemical structures are elucidated. However, such components probably should be at least controlled within the domain of the process parameters limits. The excipient manufacturer would not necessarily be required to reduce their amounts by performing additional processing, or by changing process parameters, because their removal could also impact other components and thus have an unknown impact on the functionality of the excipient.
2. Small molecules derived from natural materials, and small molecules obtained via synthetic routes from well-characterized chemical components:
    a. When synthetically derived, these tend to be well-characterized single molecular entities.
    b. When obtained from natural raw materials, these excipients tend to be incompletely characterized, and it is often difficult to determine the contribution of each component to excipient functionality or performance.

As stated above, despite the analytical tools available, for some excipients (e.g., polymers, minerals, and from plant and animal sources), it remains challenging—in some cases, impossible—to develop a validated chemical assay that accurately detects and quantitates each component (*3*). Likewise, it is often challenging to construct a specification with orthogonal

methods of chemical analysis that enable pharmaceutical manufacturers to account for virtually every component present in an excipient. In addition to these difficulties, an even bigger problem is the uncertainty about how to classify components detected in the excipient as either an impurity or a component that we define below as a concomitant component, which may have a beneficial effect in the use of the excipient.

Unlike most active ingredients, excipients are not manufactured with the intention of yielding a single well-characterized substance. Some excipients are manufactured by polymerization (e.g., povidone). Although the degree of variation of the polymer size within a given range can be controlled to some extent, a single molecular entity is never obtained. The range of polymer molecular weights for a given grade of povidone is specified in the Pharmacopeia, and is generally well understood. In the case of natural polymers (biopolymers), the range of molecular weights is not well understood.

Many excipients are obtained by extraction from naturally occurring materials, or from the further processing of these extracts. The purified extracts will often contain components with similar chemical structure or functional groups. In other situations, there may be unrelated components that cannot be easily separated from the main components in the extract. In addition, the amount of each of these components often varies based on factors such as species, regions, climate, weather, and/or processing technique. The many variables related to the starting material and its processing can lead to differences in excipient composition from batch to batch, or changes in composition over time. Such changes may eventually impact excipient performance and drug product performance.

Manufacturing of excipients must take place in accordance with appropriate Good Manufacturing Practice (GMP) (*4*) such that excipient composition and impurities can be adequately reproduced and controlled, respectively. Thus, excipient manufacturers need some guidance from pharmaceutical manufacturers to determine which substances in the excipient need to be controlled as impurities. Uncertainty or disparity among end users makes setting of specifications challenging in terms of classification of a substance as an excipient impurity as opposed to being part of the excipient composition. As the composition of Oleyl Alcohol NF was revealed with introduction of a gas chromatographic method for the *Assay* and *Limit of Related Fatty Alcohols* test, there were two distinct groups of drug manufacturers, although, who used Oleyl Alcohol within the range specified in the monograph, NLT 75.0% and NMT 102.0%, had completely different preferences in regards to the content of the major and minor components and views on how to classify those minor components. 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.

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. Concomitant components of an excipient include substances that either are known to promote excipient function or have an unknown contribution to excipient function, and are clearly not deleterious to excipient quality.

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.

Chromatographic methods often reveal that other components are present in an excipient in minor amounts. 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).

One area of confusion related to excipient composition is the relationship between the compendial title (official name) and the actual composition. This is particularly troublesome for excipients that almost always have a multitude of related components present due to the nature of how such excipients are derived, even after undergoing chemical transformations and purification. For example, Microcrystalline Cellulose NF contains α-cellulose (cellulose I), B-cellulose (cellulose II), hemicelluloses, sugar residues (from the hydrolysis step), ammonia residues, and residues from the pulping process, together with components carried over from the original cellulose source that were not removed by subsequent processing. For such excipients, the compositional profile may look significantly different when comparing samples of the same excipient from different sources or manufacturing processes.

Certain assay and impurity tests in excipient monographs are nonspecific and collectively detect related substances. In these cases, the reporting consists of stating the amounts semi-quantitatively by reference to a single component (e.g., aldehydes, reported as formaldehyde; amino groups, reported as nitrogen).

An important goal is to provide, if possible, a specific assay in each excipient monograph. Chromatographic assays, where appropriate, enable measurements that, at the very least, provide information on the excipient composition, including how this composition may vary. Since many excipients considered for monograph updating have variable amounts of main components, assay specifications will dictate a range or a limit (upper and/or lower) for the percentage of each major component or sum of

major components. Levels for some of the closely related chemical components present in minor amounts may also be similarly addressed either by specifying ranges or limits. Some examples include Sesame Oil NF, Castor Oil USP, Hydrogenated Castor Oil NF, and Lecithin NF. Although minor components might not be specified, these substances can be identified in an assay method and, if desired, measured using chromatographic retention times. An upper limit in the specification should not imply that a substance is an impurity unless justified based on a known, inverse correlation between the presence of the substance and product quality/patient safety as discussed above.

Given the large number of excipients listed in *USP–NF* and their complexity, the Excipient Impurities Joint Subcommittee is proposing the following set of definitions to aid in classifying excipients and to improve contrast between acceptable components of the excipients and impurities in excipients. When discussing the composition and quality of any *Official Substance* (*5*), it is intended for the definitions below to apply when used as a pharmaceutical excipient.

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.
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.
Simple excipient: An excipient composed of a single main substance with a well-defined chemical structure that can be characterized well analytically.
Complex excipient: Any excipient that does not fit the definition of a simple excipient.
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.)
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*).
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 above).

One of the challenges when setting specifications is that ranges for the different substances found in an excipient are usually developed from analytical data provided by monograph sponsors. This approach represents a sampling of the market, but is not necessarily representative of all marketed sources of the excipient. The ranges tend to characterize excipients based on how they are manufactured, including how they are derived. These data tend to provide some point of reference for making comparisons, for example when one is considering supplier changes. Often these related substances are part of a homologous series of components that have very similar structures (e.g., carbon chain lengths in series that differ by two carbon atoms in excipients tracing back to oils extracted from seeds).

Additional information on the excipient composition will allow product manufacturers to monitor for differences that might indicate deviation from the norm or to make better decisions allowing them to improve product manufacturing. Each drug product manufacturer can interpret differences and decide how to take advantage of additional information on excipient composition, as in the case of Oleyl Alcohol described above.

Minor components of the excipient 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. Incomplete chemical characterization of the individual components of an excipient could be due to the inability to detect or accurately quantitate the minor components, or inability to elucidate the structure of a newly detected component well enough to compare it with other components that might also be present. As methods are improved, it is likely that additional minor components will be detected. However, it is important to remember that these minor components probably have always been in the excipient. In addition, absent e.g. safety concerns, minor components known to be present in certain excipients might not have been considered important enough to be measured and monitored.

Stearic acid and stearate derivatives (e.g., alkaline earth metal soaps and glyceryl esters), provide an excellent example, whereby the two main components, stearic acid and palmitic acid, comprise roughly 95% of the fatty acid composition; related fatty acids are known to be present but have not needed to be monitored in virtually all cases. Even in cases where a minor component has an upper limit (e.g., in a fatty acid assay), this should not necessarily indicate that it needs to be considered an impurity. Components present in minor amounts are more likely to have some effect on the performance of the drug product than to pose any safety concerns. One such example is dibasic calcium phosphate dihydrate. While it is possible to obtain a very pure material with very low levels of foreign ions, tests have shown that the very pure dibasic calcium phosphate dihydrate does not compact as well as the less pure material. The reason is that the foreign ions, when incorporated into the crystal lattice during excipient manufacturing, provide dislocations that facilitate brittle fracture. The very pure material does not have sufficient dislocations in the crystal lattice to facilitate adequate brittle fracture during manufacture of the tablets. For many tablet products, this is a key property that contributes to the excipient's performance.

Modern analytical techniques, such as the chromatographic assays that USP has implemented for certain excipients in the past and is currently investigating for others, are shedding new light on the variability in composition of many excipients. Manufacturers of drug products might not have been aware of such variability. There are many compendial excipients for which the composition is only vaguely understood, and this situation will not change barring additional testing not required for ascertaining compliance with the respective official monographs. Many of these excipients are derived from starting materials that in raw form might not be considered safe, thus some degree of purification is often necessary. Moreover, the supply chains for many of these excipients appear to be globalized and may have some degree of complexity potentially obscuring the identity of the original manufacturer or the source derivation (e.g., botanical species) of the excipient. Many excipient supply chains have the potential to be intertwined with industrial chemical supply chains such that enhanced characterization might provide a means to monitor supply chain integrity after supplier qualification.

EVALUATION OF EXCIPIENT COMPOSITION AND SETTING SPECIFICATIONS

USP–NF monograph requirements are the minimum requirements for quality, identity, and purity of the excipients. The quality, identity, and purity of each excipient are related to the safety of the excipient. A specification should adequately ensure that the excipient composition is as expected for that particular excipient, substances considered to be impurities are acceptably limited, and the excipient can, to the extent possible, be unequivocally identified to preclude use of a mislabeled excipient. Excipients that comply with the identity and purity tests and which are used within a proper context (e.g., amount and route of administration) would generally be considered safe to use.

Historically, USP has relied on the external stakeholders to submit new monographs or to support revisions to the existing monographs. However, recently, USP has been engaging its internal laboratories to fulfill this task. In both approaches, one of the many requirements for accepting either a submission for a new monograph or a request for revision (*6,7*) is that the excipient, for which a revision or development is initiated, or sponsor's material is used in an FDA regulated drug. However because excipients are evaluated as part of the drug aproval process it is possible that only a single manufacturing process and corresponding potential impurities, and not necessarily all possible methods of manufacturing and resultant impurities will have been evaluated for safety. As other manufacturers start making the same excipients but employ a different manufacturing process should the excipient safety profile be considered equivalent? Can we make an assumption that each manufacturer knows their product impurities and safety implications? What if they limit their testing to the procedures in a monograph that may not be specific? To address the above concerns, all excipient makers and users are encouraged to review and provide commentary to proposals, as well as provide samples of or infromation about excipients in question to USP, to ensure any specification that ultimately becomes official adequately covers the excipient in regulated drugs.

In this section, we will provide a description of a systematic approach EM1 has taken in evaluating excipient composition and in setting limits or ranges for excipients components in the monographs that have been identified in need of more specific *Assay* and/or *Impurities* tests.

This is a multistep process reflective of the complexity of the excipient composition and setting specifications for excipients that includes both a general as well as a specific approach to the evaluation of excipient composition depending on the nature of the excipient. On the side of caution, when an impurity profile or a composition of an excipient is revealed by a more specific procedure, 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 EC's general approach is to identify what those components are, if possible. However for polymeric and mixture type excipients, USP closely works with the stakeholders to address composition, concomitant components, and/or impurities. When successful, the EC considers a review of the safety data, toxicological data (LD50s for the nominal and all other components and data from TOXNET (*8*), a resource for searching databases on toxicology, hazardous chemicals, environmental health, and toxic releases), process capability, and a statistical evaluation of the impurity levels of the currently marketed pharmacopeial excipients. However, this evaluation could not be undertaken by USP without a set of samples representative of the excipient U.S market. Thus, a large range of samples would be needed to ensure that samples from as many sources and manufacturing processes for the excipient as possible are available for analysis. If the toxicological data for the nominal and minor components are similar, then the limit for the minor component can be set based on the process capability [see *Case Study 1. Fumaric Acid* (*9*)]. Additionally, FDA is often consulted to weigh in on newly identified components as was the case for Methyl Salicylate [*Case Study 2* (*10*)]. In the event there is no pertinent information on safety or toxicity of a minor component available, other Pharmacopeias are consulted, and input from stakeholders is also sought. In this instance, a limit specified in another Pharmacopeia or used by stakeholders to control variability of the excipient can be proposed for adoption. Collaboration of drug manufacturers, material manufacturers, trade associations and FDA can definitely help USP ECs develop an up-to-date monograph with appropriate impurity specifications as in the case of Polyethylene Glycol 3350 [*Case Study 4* (*11*)].

As we strive to improve the assay methods, we expect to detect more components that have always been present at relatively low levels in excipients but were undetectable or unresolvable from other components. One way to classify minor excipient components is to divide them into two groups: known and unknown. Known components are further subdivided into two subgroups, existing and new. For the existing subgroup, it is proposed that either the limits remain the same as the current monograph or they are updated based on data from representative samples. A good example of an excipient that contains an

existing and a new component is Fumaric Acid, for which the monograph was recently revised in *PF* 43(5) (*Case Study 1. Fumaric Acid*).

However, as described earlier, some of these newly detected or identified substances may be concomitant components which contribute to the generally expected functionality of the excipient. For example, as previously mentioned above, the removal of foreign ions from dibasic calcium phosphate affects its compaction properties. Furthermore, an unintended consequence of a change in composition is that the desired performance of the excipient is not realized. This is especially a concern when the performance has not been correlated to excipient composition and/or the method of manufacturing, as is often the case for excipients. The primary focus in establishing limits for newly detected components in excipients must remain on safety. It should be pointed out that the current monograph structure provides flexibility in listing impurities and components that are part of an excipient composition in different monograph sections, *Impurities* versus *Specific Tests* and/or *Other Components*. However, in order for USP to properly classify components and avoid unnecessarily referring to a specified component as an impurity, relevant information should be shared with USP by the drug manufacturers.

There are several situations in which previously unknown or unidentified components in an excipient may arise:

1. From use of a new analytical technology or methodology that shows more components than previously detected (*Case Study 1. Fumaric Acid* and *Case Study 2. Methyl Salicylate*).
2. Where the excipient is manufactured synthetically or from natural sources and an alternate source of material is, or becomes available [*Case Study 3. Deoxycholic Acid* (*12*)].
3. Intentional alteration of an existing manufacturing process potentially affecting levels of components not considered to be part of the nominal composition. For example, a change in composition might be the result of a change in the source (e.g., supplier or derivation) of an excipient starting material.

As previously discussed, all unknown components exceeding 0.1% in simple excipients and at minor to significant amounts in polymeric and mixture type excipients will be reviewed by the EC following the multistep process described above.

With the differences in source and manufacturing process potentially leading to different composition profiles there are two possible approaches to resolving these differences:

1. Have different specifications for the same excipient reflecting different composition profiles. This approach is covered by *General Notices, 4.10.10 Applicability of Test Procedures*. The recent update to the *Octyldodecanol* (*13*) monograph is a good example of this approach.
2. Have the same specifications that would include concomitant components and impurities from all sources and manufacturing processes for excipients.

There are some advantages and disadvantages of the approaches described above. However each of them will require a significant amount of time and resources when dealing with excipients coming from different sources and/or manufacturing processes.

Another consideration when setting specifications is the consistency of the composition of the excipients. Many excipients have been used for many years, and most have a use in other industries such as the food industry. However, because most excipients are mixtures of related components or other components, the composition of many of these excipients was not known precisely enough until recently. The exceptions were cases of significant problems in the sourcing, manufacture, or storage of an excipient. Overall, consistency of composition was not measurable or definable because the impurity profiles were simply not known. With the USP Up-to-Date Initiative and other advances in analytical technology and toxicology data, the issue of consistency is now relevant.

Figure 2 captures outlines of what has been discussed in this section and illustrates a decision tree for evaluating and setting specifications for components in excipients that is presented below:

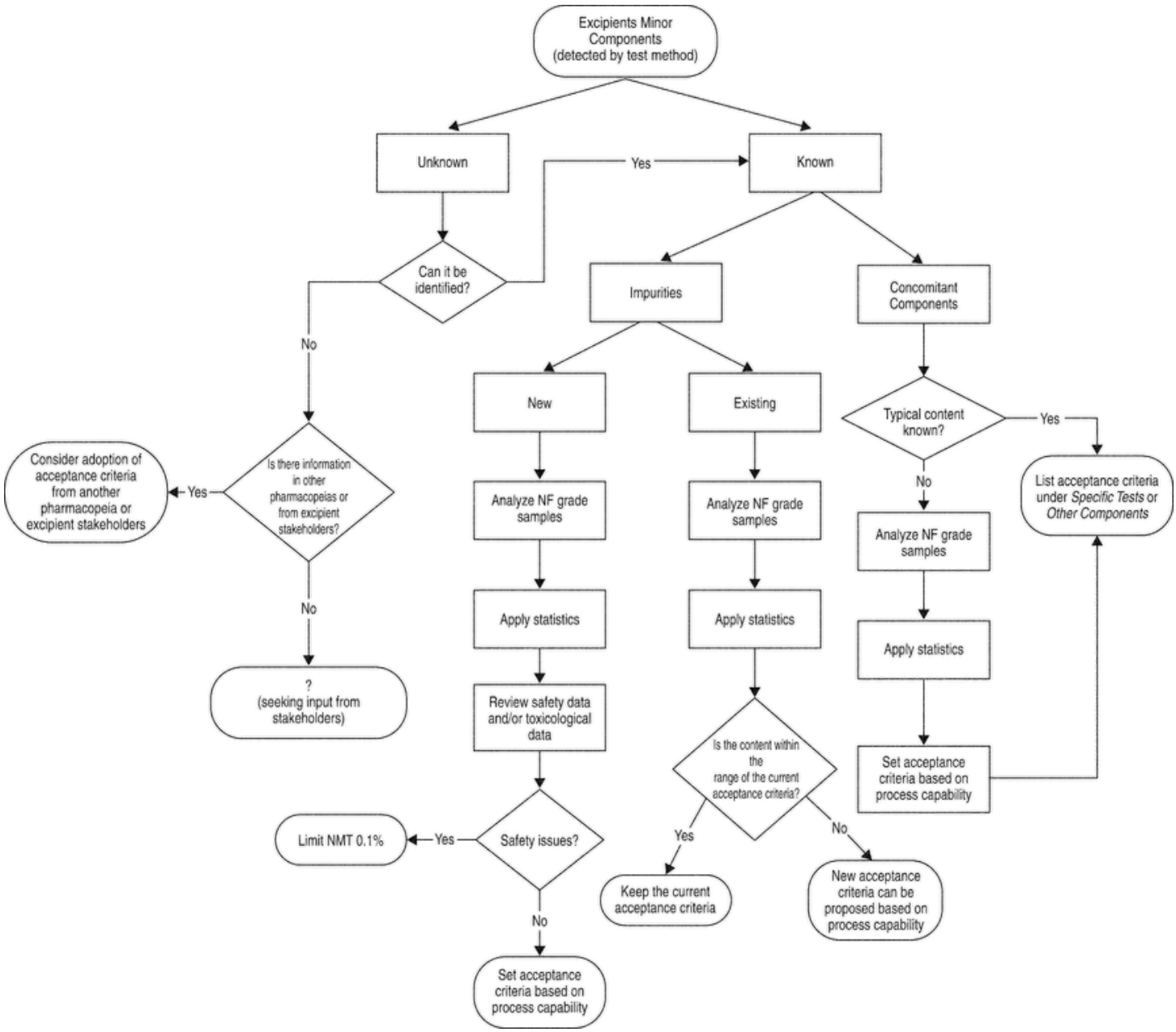
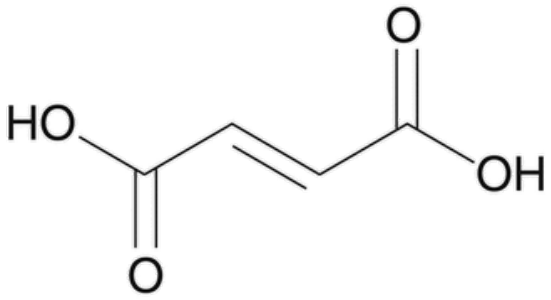


Figure 2. A decision tree for evaluating and setting specifications for components in excipients.

Case Study 1: Fumaric Acid (*9*)

Fumaric Acid is classified as a simple excipient consisting of a well characterized single major component.

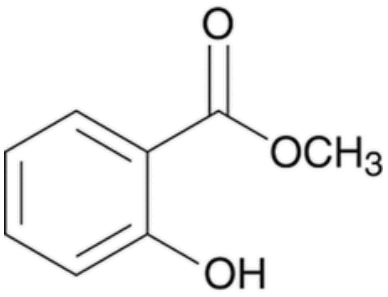


The monograph *Definition* neither specifies the source nor provides any details of the Fumaric Acid manufacturing process. However, on the basis of literature search at least two different manufacturing processes were identified. The current monograph has a titrimetric *Assay* and an HPLC-UV test for *Limit of Maleic Acid* with the acceptance criterion of NMT 0.1%. The EM1 EC recommended replacing the titrimetric *Assay* with an HPLC-UV *Assay*. Additionally, the EC proposed developing one HPLC procedure that could be employed for evaluating purity and composition of Fumaric Acid and other two related acids, Maleic Acid and Malic Acid. The analysis of 10 samples of Fumaric Acid from five different manufacturers revealed that some samples contained up to 1.0% of malic acid (new component) in addition to a minor presence (about 0.01%) of maleic acid (existing

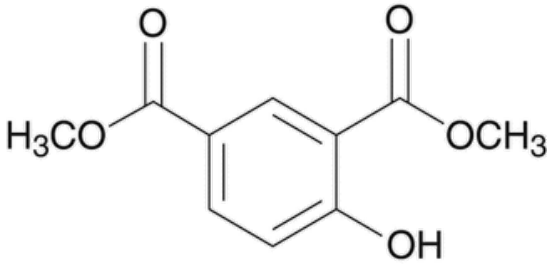
component). The variance component model was used to determine a 95% prediction interval around the mean value to set the limit for malic acid. That limit was calculated as NMT 1.1%. Because there are no safety issues with malic acid, the EC recommended setting a limit for malic acid at NMT 1.5% and keeping the limit for maleic acid unchanged at NMT 0.1%.

Case Study 2: Methyl Salicylate (*10*)

Methyl Salicylate is classified as a simple excipient consisting of a well-characterized single nominal component.



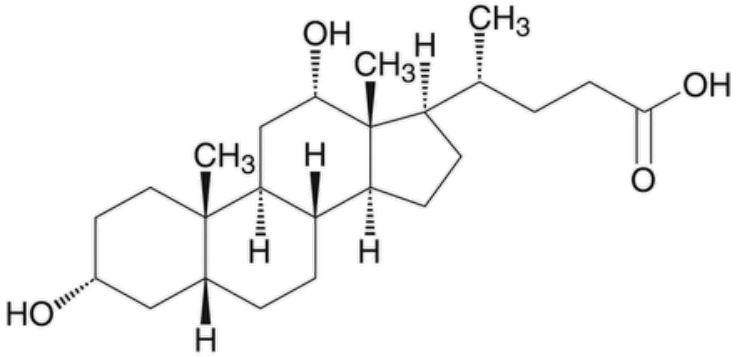
According to the monograph *Definition*, methyl salicylate is produced synthetically or is obtained from natural sources. During the modernization effort, with the assistance of the USP compendial development laboratory (CDL) the EC discovered the presence of an impurity, dimethyl 4-hydroxyisophthalate, which may be generated from manufacturing processes as a process intermediate. The USP CDL utilized LC-MS, UV/Vis, and authentic substance to confirm the identity of the impurity, and analyzed Methyl Salicylate NF grade materials from various and different manufacturers/suppliers, which are available from the market. FDA provided the EC feedback for the proposed impurity—dimethyl 4-hydroxyisophthalate.



On the basis of all the information and test sample results, the EC proposed a limit for dimethyl 4-hydroxyisophthalate as NMT 0.5%.

Case Study 3: Deoxycholic Acid (*12*)

Deoxycholic Acid is classified as a simple excipient consisting of a single well-characterized nominal component.



Even though the original monograph *Definition* did not specify the source of Deoxycholic Acid the only available source of this excipient on the market was bovine bile acids. When a new synthetic source became available the monograph was revised to replace a titrimetric *Assay* with an HPLC *Assay*. Additionally, a test for *Organic Impurities* by HPLC was added to the monograph. The sponsor of the monograph revision provided a list of impurities typically observed in the synthetic Deoxycholic Acid. Using this HPLC method, which was specific for impurities in Deoxycholic Acid of both origins, the USP lab analyzed nine samples of Deoxycholic Acid of animal origin. The analysis showed that the impurity profiles of Deoxycholic Acid from the two sources were very different. As a result, two sets of *Acceptance criteria* were included in the *Organic Impurities* of the monograph (see below).

Acceptance criteria
Deoxycholic Acid of animal origin
Cholic acid: NMT 1.0%
Total impurities: NMT 2.0%
Deoxycholic Acid of synthetic origin: See Table 2.

Table 2

Name	Relative Retention Time	Acceptance Criteria NMT (%)
3α,12β-Dihydroxy-5β-cholan-24-oic acid	0.69	0.15
3α,12α-Dihydroxy-5β-chol-9(11)-en-24-oic acid	0.87	0.15
Ethyl 3α,12α-dihydroxy-5β-cholan-24-oate	1.61	0.15
Any individual unspecified impurity	—	0.10
Total impurities	—	2.0

Acceptance criteria

Deoxycholic acid of animal origin

Cholic acid: NMT 1.0%

Total impurities: NMT 2.0%

Deoxycholic acid of synthetic origin: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria NMT (%)
3α, 12β-Dihydroxy-5β-cholan-24-oic acid	0.69	0.15
3α, 12α-Dihydroxy-5β-chol-9(11)-en-24-oic acid	0.87	0.15
Ethyl 3α, 12α-dihydroxy-5β-cholan-24-oate	1.61	0.15
Any individual unspecified impurity	—	0.10
Total impurities	—	2.0

Case Study 4: Polyethylene Glycol 3350 (*11*)

Polyethylene Glycol 3350 is 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.

Polyethylene Glycol 3350 was initially included in the official *Polyethylene Glycol NF* monograph without impurity tests for formaldehyde and acetaldehyde. Within the newly developed *Polyethylene Glycol 3350* monograph, in the *Impurities* section, in addition to inorganic impurities that can be estimated through *Residue on Ignition*, the test for *Limit of Ethylene Oxide and Dioxane* is used to monitor and limit the residual starting material—ethylene oxide and the process intermediate—dioxane that is a dimer of ethylene oxide. Both ethylene oxide and dioxane are toxic. The test for *Limit of Ethylene Glycol and Diethylene Glycol* was implemented to monitor and control ethylene glycol and diethylene glycol that are process intermediates. Ethylene glycol is generated when ethylene oxide reacts with water, and diethylene glycol is a dimer of ethylene glycol. Both ethylene glycol and diethylene glycol are toxic as well. Finally, many researches and studies reported that formaldehyde and acetaldehyde are process impurities which greatly impact polyethylene glycol 3350 product stability, and further deteriorate drug formulation because they are reactive in nature. Some additional impurities such as formic acid and acetic acid can be controlled by setting an appropriate specification for *Acidity and Alkalinity*. The Excipients EM1 EC worked with two excipient manufacturers, two drug companies, a trade organization, FDA, and the USP lab to set appropriate specifications for impurities.

CONCLUSIONS

With the modernization and updating of excipient monographs, and the move away from e.g. nonspecific titrations to chromatographic methods, it is becoming more clear that excipients typically are not small molecules, but often very complex substances requiring different types of specification to small molecule APIs. Thus, setting specifications for excipients is not straightforward. In many cases, the criteria given in USP *General Notices, 5.60.10 Other Impurities in USP and NF Articles* and *5.60.20 Residual Solvents in USP and NF Articles* cannot be applied to excipients because of the complexity of their composition. The rigid application of the term "impurity" to any excipient component present above the USP *5.60.10* threshold (0.1%, w/w) would mean that the majority of excipients available today could not be used for the manufacture of pharmaceutical finished products, with catastrophic consequences for patients. Many of the components present in excipients may be necessary for performance in different application, and are thus not impurities but concomitant components. A distinction must be made

between excipient impurities that detract from the quality of the excipient (including safety), and those components which can be present, have always been present, and may need to be present to achieve the necessary performance in the application. It must also be remembered that most excipients have been in use for many decades and are considered safe, including the levels of their concomitant components. In setting specifications in *USP–NF* for excipients, the ECs take into account the information available to them; however, it must be acknowledged that with the diversity in source and manufacture of many excipients, it may not be possible to provide specifications for all components, covering all potential sources, of a particular excipient. In addition, the link between excipient composition and excipient performance is typically not well understood. Thus, it is difficult to identify which concomitant excipient components should be controlled. This is more properly the responsibility of the excipient user since the performance requirements and limits will be application (formulation) dependent. The Excipient Impurities Joint Subcommittee is seeking feedback from stakeholders, and encourages stakeholders to submit comments on the article. In addition, the Subcommittee strongly encourages all stakeholders to complete the survey questionnaire on the USP website when it becomes available.

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REFERENCES

1. FDA and USP Workshop on Standards for Pharmaceutical Products—"Critical Importance of Excipients in Product Development: Why Excipients are Important Now and In the Future" (highlighted the importance of advancing the science of excipient selection and regulatory evaluation that impact generic drug development). February 27–28, 2017. https://www.usp.org/events-training/workshops/fda-and-usp-workshop-standards-pharmaceutical-products.
2. International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Q3A(R2) Impurities in new drug substances. 2006. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3A_R2/Step4/Q3A_R2__Guideline.pdf Accessed 5 March 2018.
3. Holloway G, Sheehan C, Wang H. Challenges and Opportunities in Developing Up-to-Date USP–NF Excipients, Part 1. *American Pharmaceutical Review*. September 30, 2015. http://www.americanpharmaceuticalreview.com/Featured-Articles/179321-Challenges-and-Opportunities-in-Developing-Up-to-Date-USP-NF-Excipients/
4. *USP 41–NF 36*. *General Notices, 3. Conformance to Standards, 3.10 Applicability of Standards*.
5. *USP 41–NF 36*. *General Notices, 2. Official Status and Legal Recognition, 2.20 Official Articles*.
6. USP Guideline for Submitting Requests for Revision to *USP–NF*: General Information for All Submissions, https://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/general-information-for-all-submissions.pdf. Accessed 5 March 2018.
7. USP Guideline for Submitting Requests for Revision to *USP–NF*: Submission Guideline for Excipients, https://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/excipients_rfr_guideline-28apr16.pdf. Accessed 5 March 2018.
8. U.S. National Library of Medicine. TOXNET. https://toxnet.nlm.nih.gov. Accessed 5 March 2018.
9. US Pharmacopeial Convention. *Fumaric Acid*. In *PF* 43(5) [Sept.–Oct. 2017].
10. US Pharmacopeial Convention. *Methyl Salicylate*. In *PF* 40(2) [Mar.–Apr. 2014].
11. US Pharmacopeial Convention. *Polyethylene Glycol 3350*. In *PF* 39(6) [Nov.–Dec. 2013] and *PF* 41(4) [July–Aug. 2015].
12. US Pharmacopeial Convention. *Deoxycholic Acid*. In *PF* 41(5) [Sept.–Oct. 2015].
13. US Pharmacopeial Convention. *Octyldodecanol*. In *PF* 40(2) [Mar.–Apr. 2014] and *PF* 42(4) [July–Aug. 2016] *In-Process Revision* and *Proposed Interim Revision Announcement*.

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