IPEC AMERICAS insider

Impure Thoughts

In the pharmaceutical world, the application of a definition developed for one purpose to other areas frequently has unintended consequences, resulting in confusion and unnecessary compliance burdens. The term “impurity” is one such example and was a subject of lengthy debate at IPEC-Americas December 8th Excipient Composition Committee.

According to “Pharmaceutical Technology” magazine, “The term *impurity* reflects unwanted chemicals that are present in APIs or that develop during formulation or upon aging of the API in the formulated drug product. The presence of such unwanted material, even in small amounts, could affect the efficacy and safety of pharmaceutical products. Several guidelines from the International Conference on Harmonization (ICH) address impurities in new drug substances, drug products, and residual solvents.”[1]

The ICH Technical Requirements for Pharmaceuticals for Human Use define an impurity as:

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

It is worth noting none of these definitions relate to either excipients or drug components. Many excipients are multicomponent in composition and often lack a specific assay. To define an excipient impurity as anything other than the (nominal) labeled entity becomes meaningless, especially when the labeled entity itself is only a minor proportion of the composition.

New analytical technologies give ever more quantitative detail of the complex multicomponent nature of many common excipients which have been in safe use for decades. Unfortunately quantification often exceeds understanding, sometimes resulting in inappropriate or unproductive activity on the part of users and regulators. Is revelation of previously unknown detail a good thing? As any lawyer will tell you, “it depends.”

---

[1] http://www.pharmtech.com/evaluating-impurities-drugs-part-iii-iii

[2] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3A_R2/Step4/Q3A_R2__Guideline.pdf

[3] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3B_R2/Step4/Q3B_R2__Guideline.pdf

[4] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf

Many excipients, especially polymers (such as polyethylene glycols or PEGs) and "naturally derived" products (such as excipients derived from fats and oils) are very complex materials which can have, in addition to the nominal labeled entity, a large number of other components comprising the commercially available material. Sometimes these moieties are referred to as "concomitant components". They "contribute to excipient performance and do not present a safety concern"[5].

Rather than being the difference of 100% - assay, as for APIs, excipient "impurities" are better described as specific entities that should not be present and/or need to be controlled for safety, toxicological or other reasons.

In the excipient world therefore, it becomes very important to keep the semantics straight regarding "impurities" and "concomitant components".

API + impurities = 100%

Excipient + Concomitant Components + impurities = 100%

In the case of APIs, the material named in the monograph is key. As mentioned above, almost anything that is not the named material is regarded as an "impurity" – that is, the named entity plus impurities equals API. For excipients however, the complexity of composition makes monograph names and contents a more difficult issue. In most cases but not all, the monograph name refers to the predominant material in the excipient but as mentioned above, there may be many other components ("concomitant components") which are not only desired but necessary for the excipient to function effectively in its applications.

So why is this suddenly a problem? The USP has merged General Notices for APIs and excipients so that which is mandated for APIs now could be construed to apply to excipients and vice-versa. If the General Notices require that an API equals the labeled entity plus impurities then this also becomes the requirement for excipients even though their composition is much more complex. No distinction is made between concomitant components and impurities.

The specific phrasing at issue is as follows:

"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."[6]

The IPEC-Americas Excipient Composition Committee therefore concluded that action needs to be taken to assure that the USP considers the following in merging the General Notices:

- A definition of "impurity" relevant to excipients is provided;
- The chemical complexity of excipients, including concomitant components, is taken into account.

[5] http://www.usp.org/sites/default/files/events/stakeholder_forums/2013/meeting-2/03b-usp-excipients-standards-setting-process-2014-06-18.pdf

[6] 6http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/USP34-NF29General%20Notices.pdf

Excipient users will need to improve their knowledge of excipient composition, which may be process/supplier dependent, and assess risk to finished product performance. This is not a simple issue that can be addressed by blindly applying the same “rules” for APIs to excipients.

The Excipient Composition Committee recommends:

- Nominating two IPEC-Americas representatives to serve on USP General Notices project team;
- Submitting a “Stimuli to the Revision Process” article to USP.

Updates on these actions will be discussed in future Excipient Composition Committee meetings and may be published in the “Insider”. Any member company employee interested in becoming involved in this issue is encouraged to notify IPEC-Americas at ipecamer@ipecamericas.org.