Identifying Impurities in APIs

This article is designed to serve as the first in a series of articles about impurities. In this one, we discuss the basics of chemical impurities and how CMOs can identify and eliminate them in API manufacturing.

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Potential Toxic chemicals and carcinogens in drugs that are supposed to treat diseases are one of the biggest problems to plague Active Pharmaceutical Ingredient (API) manufacturing. Because of this, one of the most important tasks of any Contract Manufacturing Organization (CMO) is to identify impurities before they impact the quality, efficacy and safety of drugs, as well as cause costly project delays.

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Analyzing the levels of impurities and the physical, structural and behavioral attributes of these impurities in APIs helps to identify the potential cause of variations in the finished product during drug development and formulation. It's also useful in spotting potential problems when evaluating new suppliers, changing or adding manufacturing sites, or scaling up production.

The value of data gleaned from this type of analysis will depend on the specific tests that are carried out. However, the bottom line is that spending some time on properly identifying impurities before making potentially critical manufacturing decisions will more often than not save time and money further down the line and help prevent API waste or prevent failure during clinical trials.

What are chemical impurities?

To be clear, impurities are chemical substances inside a confined amount of a sample which differ from the chemical composition of the material or compound of interest. Impurities are either naturally occurring or formed during the synthesis of a chemical compound.

It's important to note that it's virtually impossible to have a molecular substance that is 100 percent pure and free of impurities. The goal for most manufacturers is to exceed the 99 percent range.

Impurities in raw materials

Since raw materials most often have some level of impurity, it's important to properly vet suppliers to ensure the highest levels of quality. Many CMOs perform tests, in advance, on various raw materials to determine this before they are purchased or before manufacturing begins. When raw materials are being considered, many CMOs ask for a sample and perform a use test to make sure it meets the requirements.

Impurities in Process Manufacturing

Another place where impurities can come from is in the process itself. One way to look at it is, when you take "A" and "B" to make "C," the molecules undergo a chemical reaction. Although the majority of molecules will orient themselves to create "C," sometimes they create "D." This is an example of process impurities, and most firms strive for 70 percent of the desired compound if not higher.

Any impurities in the drug substance will then be introduced into the drug product. Once they are identified the next questions that arise are:

- Is it okay to have this compound in the drug product as an impurity?
- Is the safety of the patient at risk?
- Is the quality or the performance of the drug product compromised by the presence of this compound?

How do you evaluate the risk?

During root cause analysis to evaluate the impact of an impurity on drug quality and safety, the first question that pops up is: What is it? At first this appears to be an easy and straightforward question but it may turn into a nightmare for the analytical chemistry department. For them, it means that the in-house validated process is not under control, and requires a complete shift in priorities because of the high urgency of the problem.

The origin of the compound may also determine which guidelines to follow in the final evaluation of the drug impurity. Relevant guidelines include ICH Q3A (Impurities in New Drug Substances), ICH Q3B (Impurities in New Drug Products), ICH Q3C (Impurities: Guideline for Residual Solvents), and ICH M7 (Assessment and control of DNA reactive impurities in pharmaceuticals to limit potential carcinogenic risk).

What amount of risk may be okay?

According to ICH guidelines, **if there are impurities in the range of .15 or higher, or compounds that are less than 98 percent pure, you need to identify the impurities** and evaluate them for potential toxicity.

Since a certain amount of impurities are considered okay, at what level do CMOs decide to move ahead? Basically, if the presence of a compound – at the detected concentrations – would pose an unacceptable risk to the patient, or if it would seriously compromise the quality, it'or efficacy of the drug product, it is clear that necessary steps should be taken to reduce, or it's important to eliminate the presence of this impurity. Alternatively, simply meet one of the relevant ICH guidelines mentioned previously.

In a lot of cases, however, the presence of the compound may not pose any safety, quality or efficacy issues for the drug product. In that case, proper documentation of the impurity (its identity, concentration, toxicological evaluation and quality impact) may be sufficient.

Identifying and eliminating as many impurities as possible is key to safe and successful product commercialization. Properly vetting suppliers and conducting testing throughout process manufacturing

can identify impurity levels before they result in the loss of costly raw materials and the need to duplicate key steps.

Impurities are a fact of life when it comes to API manufacturing – what's important is how to identify them and eliminate or reduce them. We will be writing more on this topic but, in the meantime, if you have questions about impurities, including our experience in managing impurities, please call us at (978) 462-5555.