Dealing with the Unexpected in API Development

Questions to ask about your project manager

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The goal of Active Pharmaceutical Ingredient (API) development is to develop a quality, safe and robust process that will eventually bring the API to market with the hope of improving or saving people's lives.

When developing an API, the research scientist's goal is to find a route that is robust, safe and scalable, while also providing an optimal route to provide the best yield and purity. Route selection is critical and can be one of the biggest issues in development if the best route is not chosen early on.

Some companies are so eager to have product begin clinical trials that they want to rush through the R&D development phase.

This is a big mistake.

This article is intended to provide an overview of some of the unexpected developments in a drug discovery project.

While no one wants to take on what seem like unnecessary costs, the costs associated with the initial routing, familiarization or optimization of a process can be well worth it in the long run while short cuts may end up costing more and causing unnecessary delays. During the R&D phase, there are unexpected challenges, high costs, long lead-times and uncertain outcomes.

The R&D team is in charge of determining the starting materials used – from the quality specifications to the vendor they are ordered from. When the process is transferred to GMP, it is important to use the same source and quality of the starting material to ensure consistency. As it is, R&D may run into unexpected issues and problems that need to be solved along the way to ensure a successful technical transfer from the R&D facility to the GMP group.

6 Issues That Can Arise During API Manufacturing

1. Unknown impurities or a larger-than-expected yield of impurities is produced during scale up. Sometimes, scaling up can produce unexpected results, such as new impurities that weren't present during smaller-scale production or the amount of an impurity can increase significantly. At that point, the R&D team needs to examine each step to determine if they can eliminate or reduce the impurity to the expected level.
2. A key starting material may not work as intended. In some cases, the team needs to evaluate the grade or supplier to get the intended results. While it doesn't happen often, we have encountered problems when the initial work was conducted in a different facility; in rare cases, the other provider took short cuts that were not documented or otherwise fudged some of the

factors that produced the issue when conducted under cGMP. We've had to re-do the process to make sure the results we produce are consistent.

3. The initial process may not be scalable. This requires re-evaluating the process, including determining whether there are mistakes or if the master batch records are sloppy. Another question could be to find out if there is larger equipment available that will mimic the R&D size?
4. Time needed in production. A major question is the stability of the material produced. In the quest to get material to the next step, sometimes teams will avoid asking whether the product is stable enough to be held or will it degrade? For more about stability studies, check out a recent blog on the topics.
5. Wrong temperature. People who have experience baking know that you could follow all the steps correctly – but if you use the wrong temperature – too high or too low – could impact the product quality.
6. Poorly defined Critical Process Parameters (CPPs). CPP is part of Quality by Design (QbD) – as we've written about QbD here – and refers to a "process parameter whose variability has an impact on a CQA (Critical Quality Attributes) and therefore should be monitored or controlled," according to the FDA. There are a lot of variables here that need to be evaluated – such as particle size, moisture content, mixer load level, order of addition, discharge method, blend uniformity – all these, if not clearly defined ahead of time, could lead to major issues during scale up.

Unexpected challenges could be anything from choosing the wrong route and starting over, to getting a great process and in the end unable to identify the impurities. It is important for the R&D scientist to work closely with the Method Development team to ensure they have analytical methods that can be relied upon and work for their intended use. The Scientist may think they have a super product, but once tested it could fail appearance (possibly particulates), or assay is low, residual solvents high, etc. In the land of R&D, expect the unexpected!

We have also written extensively about analytics. Check out these articles: "Key Questions To Ask Your CMO About Their Analytical Capabilities," "Identifying Impurities in APIs," and "Do's and Don'ts of API Technology Transfer in Phases 1, 2 and 3 Clinical Trials." If you have additional interest in analytics, and how to deal with the unexpected during API manufacturing, please call us at (978) 462-5555.