What Could Possibly Go Wrong in API Development?

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- PCI Synthesis

It's Not So Much What Happens But How You Handle It

The quality of Active Pharmaceutical Ingredients (APIs) has a significant effect on the efficacy and safety of medications, and as such, poorly manufactured or compromised APIs can result in serious issues, such as illnesses or even death.

Since APIs are essentially the lifeblood of commercial drugs, the number-one goal of Contract Manufacturing Organizations (CMOs) and pharmaceutical firms is to develop a safe and robust process that will eventually bring the API to market safely, effectively and as quickly as possible.

To accomplish this, the research scientist's job is to identify the process, or development route that is robust, safe and scalable, while also providing a path that leads to the best yield and purity. This route selection is critical. Yet, I would bet that no process chemist – ever – said that the route to drug development and commercialization was easy and without a single bump in the road. As the famous quote goes, "the best laid plans of mice and men often go awry." Sometimes, even with the best route selection, proper testing and method development, problems can occur through no fault of the scientists or the processes.

Six Issues That Can Arise During API Manufacturing – and How to Resolve Them

Unexpected impurities. Sometimes, unknown impurities or a larger-than expected yield of impurities is produced during scale up. The very process of 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.

Problems with starting materials. A key starting material may not work as intended, so in some cases, the team may need to evaluate the grade or supplier to get the intended results. While it doesn't happen often, sometimes if the initial work was conducted in a different facility or the other provider took short cuts that were not documented, the CMO would need to re-do the process to make sure the results produced are consistent.

The initial process may not be scalable. This would require re-evaluating the process, including determining whether there are mistakes or if the master batch records are sloppy. Another step to take may be to find out if there is larger equipment available that will mimic the R&D size.

Time needed in production. A major focus should be on 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 if it has the possibility of degrading.

but if you use the wrong temperature – too high or too low – it could impact the product quality.

Poorly defined Critical Process Parameters (CPPs). CPP 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, order of addition, filtration method, etc. All of these, if not clearly defined ahead of time, could lead to major issues during scale up.

Expect the Unexpected

Unexpected challenges could really be anything from choosing the wrong route and starting over, to getting a great process and in the end being unable to identify the impurities. For these reasons, it's 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 he has a super product, but once tested it could fail for low assay, residual solvents, impurities, etc.

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. In the land of R&D, the mantra is, expect the unexpected.

A structured approach also requires that companies don't look for shortcuts or ways to streamline the critical processes. 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.

The API market is flourishing, thanks to expiring patents on global blockbuster drugs and an increase in the adoption of generics, among other factors. As competition heats up, drug developers and manufacturers need to focus on sound and steady processes and testing, while anticipating that problems can and most likely will occur despite their best efforts. The key is in recognizing the possible challenges and having a game plan in place to quickly get back on course on the road to product commercialization.

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