

How Product Failures are Related to Raw Materials

Much effort is directed at establishing the specifications for the active ingredient and the final product during the product development cycle. This is very important and highly scrutinized by the reviewing agencies, but many manufacturing delays and production lot failures are attributable to problems with the non-active raw materials used in the product especially for implantable and controlled delivery devices.

While the reasons for the failure of the non-active raw materials in a final drug product are often straight forward and easily diagnosed after the fact, it is the false assumptions and poor practices that set the stage for these problems. There is an ascending hierarchy of false assumptions and poor practices about the use and qualification of raw materials that ultimately are responsible for these failures.

Use of non-GMP Raw Materials

By definition, any material manufactured in a GMP-compliant manner is done so in a way that the process and final product are controlled and reproducible. There is also the expectation that the process and materials used will not be arbitrarily changed or even changed without prior determination of their impact. This is not necessarily the case when material is manufactured for commercial purposes. Many implantable and controlled delivery manufacturers use materials in their products that are produced by commercial manufacturers and are not GMP-compliant. The real problem with this approach is that the material used during development and product development may suddenly change and cause the product to fail specifications due to formulation changes implemented by the raw material supplier. These manufacturers usually do not notify clients of changes. This problem is exacerbated by the practice of using only one or two lots of material during product development and clinical studies so that lot-to lot differences are not examined until well into the product development or manufacturing phase.

Adopting Manufacturer's Specifications

The manufacturer assigns specifications to ensure consistency of the material from lot to lot. But the boundaries of what any particular manufacturer determines to be consistent can be, and often are, much wider than the boundaries that are acceptable for GMP manufacturing purposes. Many times the manufacturer is making the material for a different use by the majority of its clients than the ones that the implantable/controlled delivery device manufacturer intends. If the manufacturer's specifications are inadequate for a GMP-manufacturing process the final product may fail lot clearance while the original material was accepted for use because it was within specifications. This approach of adopting the manufacturer's specification often stems from a sense of inadequacy in defining the material specifications in the first place. By not confronting the problem of defining adequate GMP raw material specifications

early in the process, many implantable/controlled delivery device manufacturers are forced to confront this issue later in the development process when their time and effort are better used with other activities.

Adopting Manufacturer's Test Methods

With few exceptions (such as ASTM) there are no universal standards for the establishment and use of test methods for commercial manufacturers. These manufacturers often employ test methods that would be considered non-validated or, in some cases, incapable of even being used reproducibly. Initially it seems like a logical idea to use the same methods as the manufacturer, especially if the manufacturer's specifications have been adopted. Two problems usually quickly appear: there is little or no documentation of the validation of these methods available from the manufacturer and little or no interest in their participation in transferring the methods to a client. At this point the implantable/controlled delivery device manufacturer is faced with the problem of creating and validating these methods from scratch which begs the question, why not develop and validate methods without the constraint of having the manufacturer's methods as a starting point?

Accepting Manufacturer's C of A without Testing

Through ignorance or lack of technical capability, many implantable/controlled delivery device manufacturers rely upon the raw material manufacturer's certificate of analysis (C of A). This is an easy trap to fall into when the raw material supplier is purportedly manufacturing a GMP-compliant product and reporting compendial testing results. What is not apparent without a rigorous vendor qualification and review of the supplier's testing documentation is whether the supplier is in fact performing the current version of the compendial methods, performing the methods correctly, or even performing the methods at all. A common misrepresentation by suppliers is for compliance to European Pharmacopoeia (EP) requirements. Many of the EP tests are dissimilar from their USP counterpart methods, yet only United States Pharmacopoeia (USP) testing is performed but the C of A claims compliance to both the USP and EP on the assumption that if it passes one it passes the other. A worse example is when not even the USP tests are performed but instead manufacturer or alternative tests are substituted, yet compliance to the USP and/or EP is claimed on the C of A. Many raw material suppliers that do not operate under GMP compliance subcontract their testing to contract laboratories for compendial tests to avoid the cost and difficulty of establishing GMP-compliant testing in-house. Sometimes this testing is subcontracted to reputable laboratories, but often it is not because of the raw material manufacturer's ignorance of GMP compliance in the first place.