Volume 25 Number 7
INTERNATIONAL
BioPharm
The Science & Business of Biopharmaceuticals
July 2012
ADVANSTAR PHARMACEUTICAL

Compliance Notes

Reduce Analytical Testing and Costs Without Compromising Compliance

Unnecessary analytical testing can lead to unnecessary costs.

An out-of-specification (OOS) result in the testing of a biopharmaceutical product can necessitate investigations, rework, closeouts, costly delays, and can carry regulatory implications. These costs and delays can be frustrating and may also, at times, be unnecessary. For example, testing may indicate an OOS result that turns out to be false because the testing methodology is not robust enough, specifications are tighter than necessary, or testing is being conducted for an attribute that is not a regulatory requirement. Similarly, legacy drugs may suffer "methodology creep", that is, accumulating over their lifecycles more and more testing that is not relevant to compliance.

As these examples indicate, unnecessary costs often originate in analytical testing. Costs, however, can be reduced by rigorously questioning the purpose of each analytical test and pushing the understanding of compliance deeper into the organization. Given the large number and complexity of tests that large molecule drugs must undergo, those cost savings can be significant.

Analytical methods should address the specific requirements of compliance. At every stage of development, ask what must be demonstrated, what is compliant, and whether the test data are presenting crucial information about the material or product. Except for the database of information maintained about what goes into the final product, any other information should be regarded as nice, but not necessary, to know. In evaluating the relevance of testing methods for legacy products, look carefully at exactly what was approved and why for the product. If "method creep" has occurred, roll it back. In some cases, this finding could lead to working with FDA to eliminate unnecessary tests or information. In addition, be smart about which tests, product attributes, and process parameters are submitted to FDA. One can avoid getting stuck with the cost and time of having to submit data or maintain attributes that are not relevant to compliance or product quality.

J. Michael Rutledge, RPh, PhD, and Chet Meyers, PhD, are both managing consultants at Tunnell Consulting, Inc.

THE THREE ANALYTICAL NEEDS

There are essentially three sets of analytical testing that need to be done. Those that occur during development through Phase II clinical trials, those during Phase III clinical trials through approval and the entire lifecycle of the

Photodisc/Getty Images

marketed product, and as part of in-process testing. Each set entails distinctive challenges and requires the ability to assess risk in order to determine whether a particular test is genuinely necessary.

Development through Phase II

During development through Phase II clinical trials, one needs to establish characterization of the API, the reference, and the final drug delivery form. Characterization can be particularly daunting in biopharmaceuticals. Generating references in-house may be required annually for products such as influenza vaccines. Each year, it is important to evaluate whether a particular test is necessary to generate a reference standard or is being used as a redundant safety net.

During this phase of development, before administering the drug in Phase I and Phase II clinical trials, analytics are needed to establish the product's safety, its clinical release, and clinical stability. The analytical methodology at this point need not be extremely robust, rugged, or validated—only one or two chemists, as opposed to an entire laboratory, should be required to duplicate the results. While having confidence in the methodology is important, validating rather than qualifying analytical methods at this stage may increase costs unnecessarily. Further, methodology can be modified as long as safety and efficacy remain unaffected.

The goal of this phase of development is to submit an application to FDA that will gain approval to proceed to the next steps in the clinical trial process. Data submitted should meet the requirements of compliance, but it is sometimes tempting to try to impress the agency with specifications and criteria that go beyond those requirements. A development chemist may develop a testing methodology that is capable of detecting a higher level of purity than is called for by the drug's specification. However, such tests may not be rugged and may yield false information that requires additional unnecessary testing. Further, in approving the drug, FDA may expect the highest standard that the testing is capable of detecting. Companies should review the submission to ensure that there has been no "specification creep" or "analytical creep" that will cause difficulties in the future.

Phase III clinical trials

During Phase III clinical trials through approval and the lifecycle of the marketed product, the first consideration (after safety and purity) regarding analytical methods is whether they are quality control (QC)-friendly. The QC department must be able to run the tests reliably and reasonably quickly from batch to batch. There is no need for an elaborate method that requires days to run and provides 99.9% certainty when, for example, 95% is acceptable. Equally important is that the method should not yield false failures. To ensure that the analytical method works for QC and provides accurate data, R&D and QC should regularly communicate early on in the drug-development process. With a thorough understanding of the QC needs, analytical development personnel in R&D can create robust methodologies and transfer them successfully the first time, saving time and avoiding unnecessary costs.

At this point, final characterization of the API, the reference standard, and the dosage form needs to be achieved. In addition, validation of any process (e.g., growing of the cell cultures, isolation of the active component) that will go into the application for approval should be performed. Determine what in-process testing will be critical to controlling the process. In addition to testing safety, potency, and purity at this point, some of the analytical methods adopted must be capable of stability testing to determine when the drug will go out of compliance. Finally, any analytical methodology should meet all of the appropriate pharmacopeial standards for validity (i.e., specificity, accuracy, precision, ruggedness).

Although the methodology at this point is virtually "locked," changes can be made. However, changes that require FDA approval can be costly in terms of internal resources, the costs of submission, and the costs of delay in development. Some companies submit analytical summaries instead of the full range of data, which can enable minor tweaks in methods without requiring agency approval. This approach can save time, provide more freedom to operate, and avoid the costs of submission, much in the way that quality by design (QbD) may provide the freedom to make changes within the design space of a product without having to secure prior approval.

As part of an overall strategy to control analytical testing costs, you should also review the testing for legacy drugs with an eye to "methodology creep." Sometimes, for example, the troubleshooting of a product will uncover a problem and lead to additional testing to characterize that problem. The testing can be extended to other products and become institutionalized. Over time, this approach can become enormously costly.

In-process testing

In-process testing, the third analytical set, must be sensitive enough to detect issues with the product but not oversensitive and, therefore, prone to indicating a problem where none exists. It

should also be genuinely capable of measuring either the critical quality attributes (CQAs) or the critical process parameters (CPPs). Often, much of the testing embedded in in-process applications provides information that is nice to know but may not test a particular CQA or CPP.

In assessing the value of a particular in-process methodology, has the methodology ever accurately predicted a failure? If not, then it might not be genuinely predictive. Has the methodology ever been used to determine the status of a batch and has it indicated that the batch should go forward or be put on hold or in quarantine? Has the methodology ever been used to change a batch? If a batch has been put on hold, has the methodology accurately indicated the need to fortify the batch or do some additional purification?

If the answer to all three questions is no, then one can conduct a risk assessment to determine whether the test really indicates a CQA or CPP. Further, the concept of "fail early" is a sound principle when it comes to minimizing the costs of, and recovering from, a failed batch. Sufficient testing during cell culture is cost-effective because it allows a batch to be abandoned due to contamination, low product expression, OOS growth curves, improper nutrient or gas consumption, or other problems before committing to the typically much more expensive downstream processing.

RISK ASSESSMENT

In all three analytical sets, the key to reducing costs without compromising compliance is the ability to accurately assess risk, enabling the organization to optimize resources in high-risk areas and save resources in low-risk areas. When assessing the risk of reducing or eliminating a specification or eliminating an analytical method, four questions must be asked:

- Does the specification or method provide information about the efficacy, safety, purity, or potency of the finished product? If not, the specification or method should be reconsidered.
- Has the method ever predicted or prevented a compliance issue? If not, then it is likely adding little value.
- What would be the regulatory impact of eliminating or reducing the method? Would the benefits of eliminating or reducing it outweigh the regulatory hurdles that would have to be cleared?
- What is the cost of a batch failure versus the cost of testing? Is the frequency of batch failure statistically low that it is more cost effective to "eat" one batch whereas the cost to test each batch may far exceed the cost of the one failed batch?

If the testing of each individual batch can indicate a trend that can reduce or eliminate batch failure, then it may be worth considering implementing the testing of a statistical number of batches to determine if a trend is being observed. This approach can reduce the cost of testing (occasional testing versus every batch) and reduce the probability of a failed batch.

Because FDA started promoting quality risk management as part of its 21st century cGMP initiative, risk-based approaches to all aspects of biopharmaceutical operations have become more familiar and widespread. Analytical testing should be no exception. Although early-stage development personnel do not need to be in full GMP mode, they do need to understand more fully what is required for compliance, and just as importantly, what is not required. In fact, development personnel are increasingly undergoing GMP training for just that reason. Similarly, personnel responsible for legacy products are increasingly reviewing them for accretions of unnecessary testing. As companies who emulate them will find, significant cost savings and confidence in compliance do not have to be mutually exclusive. ◆