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ICH & USP <1220>: Implementing A QbD Analytical Framework

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The International Council for Harmonization (ICH) and the United States Pharmacopoeia (USP) are currently finalizing draft guidelines that describe a new paradigm for analytical development based on the quality by design (QbD) approach used for pharmaceutical development. These guidelines describe the analytical life cycle management approach for the development, validation, and continuous monitoring of analytical procedures using QbD principles. The new chapter will become official on May 1, 2022.

Continuous monitoring of methods is a shift that represents a significant difference in thinking for drug sponsors and their CDMO partners, as they bring pharmaceutical and biopharmaceuticals products to market. Classical analytical procedures lend themselves well to these systems, and processes involving cell-based assays are also amenable but require more thought. An analytical life cycle approach offers many advantages for drug sponsors and CDMOs. It provides a structure for analytical development and expands the knowledge base to identify critical method parameters useful in streamlining robustness experiments, and it allows for continuous performance monitoring of the method over time.

Quality By Design

Over the years, many pharmaceutical companies and regulatory agencies have embraced an enhanced approach to manufacturing using a QbD model. This differs from the standard practice by building quality into the dosage form starting at product conception. Pharmaceutical development has often been a trial-and-error attempt at formulation, manufacturing, and testing. The problem with this approach is that a complete understanding of the process is often lacking. Traditionally, the quality of the drug product has been assessed by comparing analytical results to the product specification. The use of multivariate statistics and design-of-experiments (DoE) allows for a deeper understanding of what variables are genuinely critical to quality and how their interaction can enable changes to the process in real time while maintaining quality.

The development of analytical procedures used to verify the quality of the drug product has often proceeded similarly. It is not uncommon for the development chemist to initiate method development without a clear understanding of the method's goal. Typically, method parameters are developed that the chemist thinks "may work." During the validation of the procedure, we may discover that our initial approach isn't robust or stability-indicating. We start again to address failures found during the validation process. A better system would be to use QbD techniques to treat analytical development in the same vein as pharmaceutical development. With a complete understanding of the variables of the method and their interactions, we can determine a **region** where the desired goal of the technique can be attained.

Example: Chromatographic Method Development

In this article, I will focus on chromatographic methods to illustrate the implementation of USP <1220> however, the ideas can be applied to other types of analytical procedures. Official publications of USP <1220> and its companion ICH guidance Q14 are expected early in 2022.

Let's focus on the primary points of USP <1220> and its implementation. Several points are helpful for the successful implementation of the analytical life cycle management strategy:

- Knowledge management
- Development of the analytical test profile (ATP) and target measurement uncertainty (TMU)
- Development of the analytical test parameters and control strategy
- Pre-validation experiments including forced degradation and robustness
- Method development report to capture knowledge gathered about the separation
- Quality risk assessment
- Continuous monitoring of the method to detect drift from the ATP

Knowledge Management

Before establishing the ATP, information needs to be collected to determine which analytical technique is most appropriate for the product. For chromatographic determinations, evaluation of information regarding the structure of the primary analyte, the presence of functional groups (especially ionizable functional groups), pK values of functional groups, known chemical incompatibilities, the synthetic pathway, solubility, and the ultraviolet and/or mass spectrum of the analyte are some of the essential data to capture. The characteristics of the dosage form, including the matrix, will help guide the development of a method that meets the ATP. Obtaining as much information on the sample as possible is essential in developing the method and troubleshooting issues. Consultations with organic chemists can also help identify potential degradation products and impurities. The initial draft of the method development report will include all the knowledge obtained before method development begins.

Analytical Test Profile Example

The first step should be a written ATP that describes the goal of the separation and the expected tolerance interval that we wish to obtain by defining key parameters for the procedure. It is essential to establish this document to help guide the development activities. An example of an ATP for a stability-indicating assay HPLC method might look like this:

> The method is capable of quantitating primary analyte A within the range of 80.0% to 120.0% label claim with a TMU of ± 3.0% in the presence of the direct degradation product (B), excipients, and impurities.
>
> It should also be able to detect and quantitate primary degradation product B from 0.05% to 1% with a TMU of ± 0.3%.

Understanding Total Measurement Uncertainty

The TMU is based on a tolerance interval and is probably new to most analytical chemists. A tolerance interval is a bounded set of values where a particular population percentage is likely to occur with a known confidence level. In short, tolerance intervals place bounds for where a proportion of a population is likely to fall, while confidence intervals place bounds on parameters of the population. There are several ways to establish a tolerance interval, and which procedure is best is beyond the scope of this discussion. In one stimuli article, the USP has proposed using the two-sided beta content tolerance interval for ATP development.

Development Of Parameters And Control Strategy

Now that we have established the ATP and understand the goal of the separation method, development can begin. We can select an appropriate column, detector, and mobile phases that are likely to be acceptable from the knowledge we have gathered. Non-spectrophotometric detection techniques, such as evaporating-light scattering (ELSD) or a charged aerosol detector (CAD), will be required for analytes lacking a UV chromophore. Reversed-phase high performance liquid chromatography (HPLC) offers many advantages to the analytical laboratory, but it is not useful for all compounds.

Once chromatographic parameters are established that are likely to meet the ATP, the system suitability requirements and calibration model are selected. Typically, standard agreement and injector precision are required elements. Still, additional factors such as signal-to-noise (S/N) ratio, resolution, and other requirements for the method may be necessary. It may be required to expand the TMU based on the technique's capabilities. The data collected from pre-validation/development studies can support the validation.

Specificity, detection/quantitation limit, linearity, filter compatibility, and solution stability are determined, and the data included in the method qualification report. Performing forced degradation and robustness studies will also ensure compliance with the ATP. Using DoE and a partial factorial design allows for identifying critical chromatographic parameters and the interactions between those variables. Approaching robustness using these techniques can delineate an analytical design space and optimize the critical analytical control variables.Conducting a risk assessment of all components of the analytical procedure is helpful at this point for identifying possible issues that could occur during routine analysis. Accuracy studies will verify that the ATP criteria are appropriate.

Method Qualification

Since the specificity, DL, QL, linearity, etc., were evaluated and documented in the method development report, the method qualification should focus on the method's accuracy, bias, and precision. These studies will allow for the formal assessment of the tolerance limit for compliance with the ATP. It is likely that published compendial methods were developed and validated outside of this life cycle concept. Do we follow the compendial method or do we develop new methods based on the life cycle approach for these procedures? The answer is not simple and there are regulatory reasons to adopt the compendial method irrespective of how it was developed and validated. For now, it is best to focus on developing non-compendial methods as targets for the life cycle approach.

Continuous Monitoring Strategy

Continuous monitoring of the procedure is necessary to demonstrate that the method is consistently in control. Changes in instrumentation, reagents, solvents, etc., can affect the proper functioning of the procedure. Critical method parameters/attributes will determine what variables are necessary to monitor, and method monitoring is likely the most difficult to assess. The first step is to identify critical method parameters responsible for ensuring compliance with the ATP. The trending system suitability data, reportable results, etc., provide some information. Many approaches can be practical, and each company will need to evaluate the optimal strategy.

Conclusion: The Future Of Analytical Development

CDMOs have additional challenges to face for compliance with these new concepts. Often, methods are transferred into the CDMO without any validation data, making it impossible to develop an accurate ATP. The costs associated with full compliance also must be evaluated. Often, CDMOs may not have an on-site statistician to help with the complete understanding of the process, and engaging a third party to evaluate the procedure will be helpful. Additionally, training will be needed for analytical scientists to understand the statistical concepts and necessary software. A robust equipment qualification program is necessary to ensure that the analytical procedure will perform appropriately on different instruments. A structured and gradual approach to implementing the guidance is the best option for future submissions.

The overarching philosophy of the new guidance is to envision the future of analytical development and validation in the decades to come. Implementing analytical life cycle management is complex and requires careful thought and planning. One option is to establish a multidisciplinary team consisting of analytical development chemists, quality assurance, and regulatory scientists under the sponsorship of a senior management member to determine the best approach. This synergistic approach will demonstrate to regulatory authorities that the company is proactive in the design and execution of the guidance. You should now take time to digest the new guidelines and initiate training that helps development chemists understand the concept and design a plan for the practical implementation. The approach moves method development, qualification, and management away from an empirical framework to one that is based on scientific understanding — with methods that are well understood — as a product moves to commercial manufacturing.

About The Author:

Brian Glass, senior analytical consultant at Pharmatech Associates, has over 30 years' experience in the fields of analytical research and development, quality control, validation, technical transfer services, and process development. He has held senior analytical positions in private startups, established pharmaceutical manufacturing facilities, and large CMO/CDMO organizations. His career spans all facets of the drug development process for small- and large-molecule therapeutics, from preclinical to commercial products, utilizing different modes of drug delivery systems (solid dosage, injectable, inhalants, oral solutions/suspensions, and soft gel capsules). He holds a B.S. in zoology from Louisiana Tech University.