



DPT Thought Leadership Issue 7

ANALYTICAL METHOD DEVELOPMENT AND VALIDATION — A CDMO PERSPECTIVE

INTRODUCTION

Pharmaceutical drug product development can be an expensive and time consuming process. Many challenges are faced by pharmaceutical development companies including developing a scaleable, marketable formulation, ensuring safety and efficacy of the drug product and receiving approval of the drug product by regulatory agencies. In order to receive approval by regulatory bodies, the applicant must prove control of the manufacturing process as well as validate that the methods used to evaluate drug product performance are accurate and precise. For this reason, the analytical methods created during development are a key component of the Chemistry, Manufacturing and Controls (CMC) section of a regulatory filing. Inconsistencies in the analytical method can hinder product and process development, thus delaying submission for regulatory approval and thereby delaying product launch. However, a Contract Development and Manufacturing Organization (CDMO) that understands customer needs, regulatory requirements, and has a proven track record for developing and validating analytical methods can minimize developmental costs and reduce the time to market. Properly validated drug product characterization methods are necessary for regulatory filings, but can also reduce overall turnaround time during scale-up, clinical release and commercial release.

Pharmaceutical development and biotech companies who outsource product and analytical development should consider the following attributes when selecting a service provider.

The outsourcing partner should effectively:

- Assess the project scope
- Provide an accurate and complete quote
- Assess the method for the drug substance (API)
- Develop prototypes of formulations or assess pre-existing prototypes
- Develop the analytical methods to evaluate prototypes
- Perform an informal stability to assess prototype performance
- Prevalidate methods to evaluate specificity, precision, accuracy, linearity, and robustness
- Validate methods according USP, EP, FDA, ICH guidance documents and governing bodies
- Transfer and assist in the implementation of the methods in a Quality Control environment that will release the commercially approved drug product.





RATIONALE

As part of the many CMC sections (pre-formulation, formulation development, analytical method development, clinical trial manufacturing, scale-up, and regulatory submission), analytical method development and validation activities play a crucial part in the drug development process.

Analytical methods of high quality are required for:

- Active pharmaceutical ingredient (API) characterization and stability
- Drug product characterization and stability
- Excipient characterization and stability
- Setting of specifications for the drug substance, drug product and in-process controls
- Characterization of impurities and degradants
- Transfer of methods to Quality to test and release the drug product

Analytical method development often begins with an assessment of the project scope. If the project primarily involves a transfer of the manufacturing process to a new location, then the relevant analytical methods are assessed for compliance with current regulatory requirements. These may include the methods for testing and releasing the active drug substance, excipients, in-process testing, product release, and stability methods. In general, the methods are transcribed into the CDMO's format and qualified under written protocols with specific acceptance criteria. If the methods are not compliant with the current applicable guidances (e.g., ICH, FDA, EMEA), the CDMO should inform the client and recommend a plan to redevelop and validate the analytical method.

The effort required to redevelop methods may be minor or major, depending on the level of work required to bring the method into compliance. An experienced CDMO will be able to quickly assess method compliance, make recommendations, and develop a plan for redevelopment and validation regardless of how minor or major the effort. The redevelopment of methods often produces state-of-the-art, stability-indicating analytical methods that are often able to report the degradation products with a Limit of

Quantitation (LOQ) far below the required reporting (0.1%) threshold.

Method development and validation for early stage drug products is an iterative process and dependent upon the stage of product development and phase of clinical testing. For example, the FDA guidance document cGMP for Phase 1 Investigational Drugs states that laboratory tests for components and drug products "should be scientifically sound (e.g., specific, sensitive, and accurate), suitable and reliable for the specified purpose". Developing complete stability-indicating methods at the Phase 1 stage is not mandated by the FDA, however the client and the CDMO should work toward utilizing fully validated, stability-indicating analytical methods well before submission of the drug product application for regulatory approval.

In the early stages of product development (such as IND submission, Phase 1, or Phase 2), a CDMO will begin work based upon the documentation supplied by the client. This often includes an analytical method for the drug substance or a prototype drug product formulation. Generally, the CDMO begins with sample preparation procedures since most of the excipients used in semi-solid dosage forms are either not soluble in typical HPLC mobile phases or may interfere with the quantitation of the API. The CDMO then develops an acceptable assay for the API by evaluating the peak purity using a diode array detector. A pure peak assures that there are no interfering components co-eluting with the API peak. Minimal validation of the method is often performed including Limit of Detection (LOD)/Limit of Quantitation (LOQ) determination, specificity, linearity, precision, accuracy (at the target drug concentration), solution stability, and some measure of robustness. Low level accuracy is often performed with known impurities/degradation products. When no information is available on the possible degradation products, a linearity study may be performed using the API at low levels (0.1% – 2.0%).

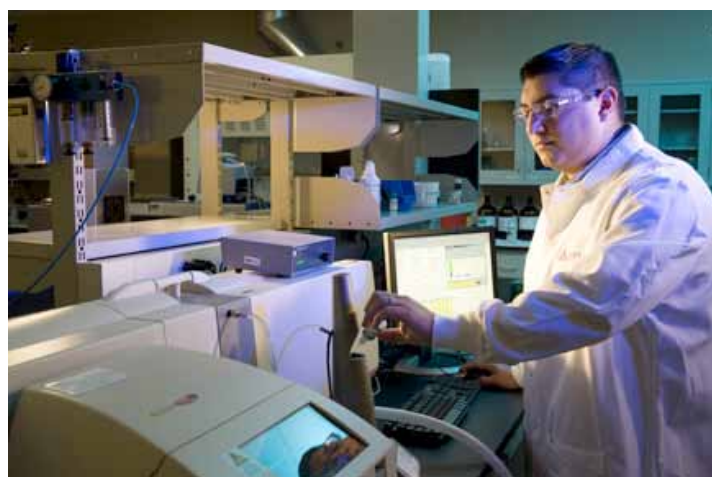
Forced degradation studies are typically performed to assess physical and chemical stability of the drug product.



This activity occurs once a final formulation is developed and optimized as changes in the formulation may affect the degradation rate and/or pathway. An experienced CDMO will help the client to identify the appropriate time to engage in this stage of the drug development process to reduce costs and ensure a quality product.

While knowledge is gained about the safety and efficacy of the selected formulations during clinical testing, additional knowledge and understanding of the stability of these formulations are gained through informal and/or formal stability studies. Furthermore, the analytical methods are performed several times to identify method related issues, such as column life and operator reproducibility. Often, the appearance of degradation products is the most useful information gained with informal stability studies. If new peaks with area % >0.1% are observed, it is important that the CDMO utilize LC/MS/MS to identify and characterize each of the new degradation products. This will assist in either determining a strategy for synthesizing those degradation products in a pure form or allow an analyst to isolate them by preparative chromatography. If more volatile components are present in the formulation, a GC/MS method can be developed to identify and characterize volatile impurities and degradation products.

full service CDMO will be able to simulate these conditions and accelerate the degradation that is likely to occur with the product at the recommended storage conditions. Generally, HPLC conditions are chosen for further optimization. Statistically designed experiments are employed to develop a “design space” to yield the maximum resolution, specificity, and robustness. Accuracy studies for the assay are performed with more narrow acceptance criteria (e.g., 97% - 103% at three concentrations covering the expected linearity range) and accuracy studies for quantitation of impurities and degradation products are conducted at the levels (typically 0.1% - 2.0%) expected to be seen during formal stability programs.



Once clinical Phase 3 trials have begun, the assay method must be stability-indicating. This is often accomplished by a forced degradation study that involves stressing the pure API, placebo, and product samples under five conditions: heat, UV/Visible light, acid, base, and oxidation. A

Specialized test procedures for determining drug release rates are developed using Franz Diffusion Cells or Enhancer Cells. The assay procedures are often used with slight modifications as a method to reduce costs. Similar strategies are used during trace level assay method development for assessing the cleaning of process equipment.

Finally, all analytical characterization methods are fully validated according to current guidance documents (e.g., ICH), and transferred to a quality control laboratory under a written protocol with established acceptance criteria. The benefit of using a full service CDMO is that they developed the method and are responsible for transferring it into their own quality control laboratory. The CDMO is also responsible for the quality of the method and robustness of the method for commercial testing and release. This allows the client to focus on a single point of contact which



ultimately leads to cost and time savings. If problems are found, the CDMO can recognize and modify issues quickly. A full service CDMO often is involved in the CMC process and can provide information quickly and easily or develop the common technical document (CTD) modules on behalf of the client for submission.

CONCLUSION

The benefit of working with an integrated service provider like DPT is that they understand that the process must be practical, consistent, and provide cost-effective analytical testing before products can be released successfully into market.

While just one step in the drug development process, analytical method development and validation is important for ensuring regulatory approval and dissemination to

the market. Establishing a partnership with a CDMO early in the development process can reduce costs and time to market by leveraging the service provider's full capabilities from conception to commercialization.

REFERENCES:

1. Validation of Compendial Methods: USP 31/NF 26, General Chapters <1225>
2. ICH Q2B – Validation of Analytical Procedures: International Conference on Harmonization
3. ICH Q3B – Impurities in New Drug products: International Conference on Harmonization
4. FDA Guidance for Industry: cGMP for Phase 1 Investigational Drugs
5. FDA Guidance for Industry: INDs for Phase 2 and Phase 3 Studies, Chemistry, Manufacturing and Controls Information

ABOUT DPT LABORATORIES:

DPT is a contract development and manufacturing organization (CDMO) providing companies the best solutions to their sterile and non-sterile pharmaceutical development and manufacturing needs through innovation, technology, and service. Specializing in semi-solid and liquid dosage forms, DPT has a reputation for quality, unmatched technical expertise, extensive manufacturing capabilities, and an exemplary regulatory compliance record. With five cGMP facilities in San Antonio, Texas, and Lakewood, New Jersey, DPT offers full-service outsourcing solutions, including stand-alone development, site transfers, state-of-the-art manufacturing, packaging, and worldwide distribution.

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