

HPLC serves as an important analytical tool in drug development and manufacturing. Assuring successful transfer of HPLC analytical methodology from Research and Development (R&D) to manufacturing and quality operations is key to the commercial manufacturing and launch of pharmaceutical dosage forms.

Introduction

High performance liquid chromatography (LC) serves as the main stay analytical technique in pharmaceutical development and manufacturing. LC is used in most every facet of activity associated with the research, development and commercialization of pharmaceutical dosage forms. Starting with the inception of the drug discovery process through compound selection and ending in commercial manufacture and launch of pharmaceutical dosage forms, LC serves as the single most important analytical tool used to assure the successful transfer of analytical methodology from Research and Development (R&D) organizations to manufacturing operations. A prerequisite for the successful transfer of an LC analytical method is the existence of validated LC method and finalized pharmaceutical dosage form. In general the timing of the transfer usually occurs at the end of phase II clinical studies or at the transition from phase II to phase III studies. Before the commencement of any method transfer activities a method transfer protocol must be implemented. The essential elements of such a protocol include a listing of materials and instrument that will be used, test method, number of batches to be tested and acceptance criteria. The transfer process concludes with an analytical method transfer report that demonstrates the unequivocal transfer of technical knowledge need to successfully utilize and run the method.

Validated HPLC Methods and Finalized Dosage Form(s)

The key prerequisite prior to the method transfer is the existence of a validated LC method and finalized formulation dosage form(s). A validated LC method is necessary since the data generated using the LC method serves as the basis for determining whether a transfer has been successful or not. The validation of the LC method parallels dosage form development activities. Method validation progresses from a Tier 1

to Tier 2 method, which has limited validation, to a more extensively and fully validated Tier 3 or Registration Method. A Tier 1 and 2 method is employed during the preformulation stages of dosage form development where emphasis is usually on speed. Consequently, the method may only have very limited validation. Typical limited

method validation at the Tier 1 and Tier 2 stage cover linearity, range, accuracy, specificity, precision and limit of quantitation (LOQ). Since at the Tier 1 and Tier 2 stage authentic samples of potential degradation products may not be available, the LOQ and accuracy are established using the API. In later phase development, when authentic samples of potential degradation are available and the dosage form has been optimized, a more extensive validation of the LC method is performed. This validation includes linearity, range, accuracy, specificity, precision, robustness, solution stability, range, repeatability, limit of detection (LOD) and limit of quantitation (LOQ).

Goals of the Analytical Transfer

The transfer goals encompass two areas; first to ensure that analytical methods developed in one lab can successfully be executed in an other lab, and second to enable the receiving lab to accurately and independently determine the quality of batches manufactured. Transfer is achieved when comparative testing between the lab that developed and validated the method and the lab receiving the method is successfully demonstrated.

Methods Transfer Protocol and Acceptance Criteria

A method transfer protocol is implemented prior to the commencement of any kind of comparative testing. A typical method transfer protocol will contain a number of sections which include an introduction, materials and supplies, treatment and disposition of the data, acceptance criteria and method acknowledgement.

The Introduction section of the method transfer protocol defines the objectives of the transfer. It unambiguously identifies the originator lab where the method was developed as the Reference lab and the other lab as Recipient or Receiving Lab. A description of the dosage form must also be presented here. Since at least three batches of each dosage strength must be tested, this section may also include arguments for bracketing of the tests. This is clearly the case when dose proportionality exists among the different dosage strengths, and that further it can be demonstrated that the analytical sample preparation procedures are identical or similar for all the dosage strengths. For example, in the case where 10 mg,

15 mg, 20 mg, and 25 mg represent the finalized pharmaceutical dosage form, this section would establish the rationale for testing only the 10 mg and 25 mg strengths.

The Materials and Supplies section describes the materials, standards and reagents that should be used as part of the method and method transfer. This section may recommend the use of certain reagents and standards and the from the purchasing of them from a specific vendor to minimize any potential influence of inherent variability in batches and material sourced from different vendors.

The Treatment and Disposition of Data section establishes the mechanism by which LC data is assessed as having passed or failed the pre-determined acceptance criteria. It must also provide specific guidance for handling "out of specification (OOS)" or "out of expectation (OOE/OOT)" issues and procedures for reporting and archiving of the data generated.

The Acceptance Criteria section enumerates the criteria by which results will be evaluated as having fulfilled the requirements of the transfer. Since the interpretation of acceptance criteria is generally based on some type of statistically evaluated value, an important aspect of this section is the inclusion of clear instructions regarding the number of batches to be tested and the number of replicate determinations from each batch required for the appropriate statistical treatment.

The Method acknowledgement section is intended as a means of capturing feedback and suggestions from discussions with the receiving lab prior to the commencement of the transfer activities. A method can sometimes be further optimized based on feedback from discussions to address special concerns or to accommodate well established procedural practices at the participating lab.

The Analytical Transfer Report

When the acceptance criteria is met for the LC method being transferred, a report is issued demonstrating that the receiving lab is fully trained and qualified to perform the method. This report details that all the acceptance criteria requirements have been satisfied. The report includes a listing of all results in the format stipulated in the protocol. It also includes a listing of all equipment used by all labs for the transfer.

Conclusion

Demonstration of a successful LC method transfer relies on a validated LC method. The transfer is accomplished by the comparative analysis of several batches by both the originating lab and receiving lab. Statistical evaluation of data generated using the LC method against pre-determined acceptance criteria resolves the issue of whether or not the transfer has been successful.

About the authors

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