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Review

Assay validation and technology transfer: Problems and solutions

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ABSTRACT

In the industry of fine chemicals, including pharmaceutical and agricultural chemicals, analytical tests are performed by production departments or contract research organizations at some stage in the research and development of products. These external organizations are required to maintain the capabilities to perform analytical tests using methods that are equivalent to or better than those specified by analytical method validation. For this reason, transfer of analytical procedures to an alternative site becomes necessary.

In this review, the relationship between transfer of analytical procedures and assay validation is introduced, focusing on analytical procedures that include HPLC.

Contents

1. Introduction

In standard tests of fine chemicals, including pharmaceutical and agricultural chemical products, various basic data obtained in the development stage, including basic properties of the compound to be analyzed, are reflected. For example, test items and operation methods are selected according to the physical properties such as volatility, solubility, stability, and ultraviolet absorption, as well as the dosage form. After determining the analytical conditions through optimization, the analytical capabilities of the selected test methods are assessed. This process is called "validation of analytical methods," which provides the basis for consistency with standards and reliability of data. In this case, however, the analytical capabilities are ascertained in the research and development stage of a product life cycle, and only

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assessment results are obtained at the laboratory that performs the validation.

At some stage in the development of products, analytical tests need to be performed at manufacturing sites to prepare for testing of compliance with regulations such as GLP and GMP, as well as actual production at contract organizations. At this time, transfer of technologies to contract research organizations or production departments becomes necessary.

A receiving laboratory is required to maintain an ability to perform analytical tests that is equivalent to or better than that specified by the analytical method validation described above. For this reason, transfer of analytical procedures becomes necessary, irrespective of whether the tests are performed in-house or outsourced to external organizations.

Thus, the need for transfer of analytical procedures occurs very frequently, but there are few documents that can be used as general guidelines for the direction of technology transfer [1]. In addition, the style of technology transfer and parameters to be used are considered to vary from company to company because circumstances vary, and to what extent validation should be performed at the receiving laboratory at the time of transfer of analytical procedures is often unclear.

The purpose of this article is to introduce the relationship between validation and transfer of analytical procedures that include high performance liquid chromatography (HPLC), an analytical technique commonly used in quality assurance tests, focusing on the present status in the pharmaceutical industry.

For more information about validation and assessment procedures, refer to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Harmonised Tripartite Guideline: Validation of Analytical Procedures: Text and Methodology Q2 (R1)[2].

2. Style of technology transfer

In 2000, the Analytical Research and Development Steering Committee (ARDSC) of the Pharmaceutical Research and Manufacturers of America (PhRMA) held a workshop on transfer of analytical procedures associated with pharmaceutical products (Pharmaceutical Research and Manufacturers of America Analytical Research and Development Workshop, Wilmington, Delaware, 20 September 2000), which included discussions on Acceptable Analytical Practice (AAP, a guidance document for appropriate technology transfer) [3].

In the AAP, the following three approaches to technology transfer are introduced:

(1) Comparative testing at the transferring and receiving laboratories.
(2) Validation of only some analytical parameters, such as the accuracy, specificity, and limit of quantitation (LOQ), at the receiving laboratory (partial validation).
(3) Revalidation or full validation of all analytical parameters at the receiving laboratory.

Technology transfer may be omitted if any of the following criteria are met (transfer waiver):

- The receiving laboratory already is testing the product and is thoroughly familiar with the procedure(s).
- The new product possesses a comparable composition or concentration of active pharmaceutical ingredient(s) relative to the existing product (Analytical Method Extension).
- The analytical method(s) are the same or very similar to the methods that are already in use.
- The validation report encompasses the new methods.
- Personnel who developed the methods move to the receiving laboratory.
- The new methods involve changes that are not substantial (e.g., changes in sample preparation procedures or changes in calculation formulas).

The basic approach to technology transfer described in this guidance document is comparative testing at two or more laboratories. An alternative to comparative testing is to involve the receiving laboratory in the validation of the method to be transferred. After the validation is completed, the receiving laboratory is considered qualified to perform the method.

United States Pharmacopoeia (USP) has also published "Transfer of Analytical Procedures" in a new General Information Chapter <1224> on the USP35 [4].

In these documents, however, only general principles of validation are presented, without any examples such as when to perform validation. The acceptance criteria for comparative testing are also unclear [5].

3. Validation of analytical methods in technology transfer

According to the Eurachem Guide [6], the extent of validation or revalidation required will depend on the circumstances in which the method is going to be used, including the laboratory, instrumentation, and operators, but examples of specific circumstances are not presented.

The guide states that validation of analytical methods is needed when:

(1) New method developed for particular problem.
(2) Established method revised to incorporate improvements or extended to a new problem.
(3) When quality control indicates an established method is changing with time.
(4) Established method used in a different laboratory, or with different analysts, or different instrumentation.
(5) To demonstrate the equivalence between two methods, e.g. a new method and original method.

In technology transfer, an established method is usually used in a different laboratory, by different analysts, or with different instrumentation. Therefore, of the above cases, (4) can be a major problem, as it is not clear whether the receiving laboratory always needs to perform revalidation in such cases.

As described in Section 2, the forms of analytical method validation are as follows: (1) full validation, (2) revalidation, and (3) validation of only some analytical parameters (partial validation). The level of intra-laboratory reproducibility between two or more laboratories, including the receiving site, may also be determined [7].

In any case, whatever method is used, there should be no problem as long as appropriate analytical parameters are chosen according to the relationship between laboratories and characteristics of the method.

Test items may vary depending on the type of the analytical method and characteristics of the sample. It will be necessary for the sending and receiving laboratories to agree on whether all items or only specific analytical parameters should be validated.

For example, when methods for impurities/degradation products/residual solvents are transferred, validation of the specificity, limit of quantitation, and limit of detection (LOD) is critically important. For the transfer of content uniformity tests, it is desirable to ensure precision.