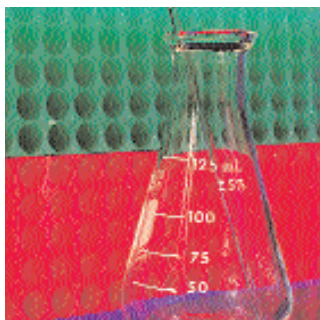


Pharmaceutical Research and Manufacturers Association Acceptable Analytical Practice for Analytical Method Transfer

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This article presents the collective views of the Analytical

Research & Development Steering Committee of the Pharmaceutical Research and Manufacturers of America (PhRMA) about the topic of **analytical method transfer**. These views were presented during PhRMA's annual workshop held in September 2000.

Stephen Scypinski, PhD, Darryl Roberts, PhD, Mary Oates, PhD, and Joseph Etse, PhD, were chosen by the Analytical Research & Development Steering Committee of the Pharmaceutical Research and Manufacturers of America (PhRMA) to draft the acceptable analytical practice guidance document.

The transfer of analytical methodology theoretically is a relatively simple operation. In its most common form, analytical method transfer qualifies a laboratory to use a test procedure. The process is driven by compliance and can be governed by both a statistical and practical treatment of the resulting data. Robust transfers begin with validated methods, as described by McGonigle (1). The transfer must be completed successfully for the receiving laboratory to obtain "reportable data," implying that these data may be used in a CGxP context.

The importance of analytical transfer was underscored by the Analytical Research and Development Steering Committee (ARDSC) of the Pharmaceutical Research and Manufacturers of America (PhRMA) during its annual workshop held in September 2000 (2). At this meeting, representatives from PhRMA member companies met with facilitators to draft an acceptable analytical practice (AAP) that can function as a suitable first-step guidance document for conducting successful method transfer activities. The focus of the AAP is to provide such guidance and to clarify the essential elements that embody a complete and compliant transfer. The AAP described in this article is intended to apply to all analytical method transfer activities from all transferring groups and combinations such as R&D to quality, R&D to R&D, and so forth. This guidance does not apply to microbiological methods or to transfers conducted to FDA laboratories for the purposes of method trials connected with regulatory dossier approval.

Types of method transfer

Method transfer is defined as the process that qualifies a laboratory to use an analytical test procedure. The most common variations of method transfer are comparative testing, covalidation between two laboratories or sites, complete or partial method validation or revalidation, and the omission of formal transfer, sometimes termed the *transfer waiver*.

Comparative testing. Comparative testing is the most common form of method transfer in the pharmaceutical industry. It involves two or more laboratories or sites executing a preapproved protocol that details the criteria by which the receiving laboratory is deemed to be qualified to use the method(s) being transferred. The resulting data are compared with a set of predetermined acceptance criteria. Comparative

testing also is used in other scenarios during development and postapproval, including other manufacturing sites and contract research organizations.

Covalidation between two laboratories. An alternative to comparative testing is to involve the receiving laboratory in the validation of the method to be transferred. By definition, a laboratory or site that performs validation experiments is qualified to run that method routinely. To perform such a transfer, one must identify which validation parameters are to be generated or challenged by the sending and receiving laboratories. A reasonable approach is to involve the receiving laboratory in the interlaboratory qualification, thereby generating a matrix of data that summarizes the suitability of the testing site, analyst, date of analysis, and instrumentation for exercising the analytical test procedures. By fully describing the experimental design for the validation exercise and including the resulting data in the method validation report, it is possible to have this document stand as proof of transfer of the analytical test procedure.

Method validation and/or revalidation. Another option for accomplishing method transfer is for the receiving laboratory to repeat some or all of the validation experiments. After validation is completed, the second laboratory is deemed qualified to perform the method. The choice of validation parameter(s) depends highly on the type of method being transferred. For example, content uniformity assays to determine consistency of product potency depend heavily on the precision of the method.

Transfer waiver. Certain situations might warrant omitting conventional transfer qualification experiments altogether. When a transfer waiver is applied, the receiving laboratory can proceed to use the analytical test procedures under discussion without generating interlaboratory comparative testing data. To proceed without generating such data, one must document the reasons why this action was taken. Examples of these reasons were discussed by PhRMA workshop attendees; they include the following:

- The receiving laboratory already is testing the product and is thoroughly familiar with the procedure(s).
- The new dosage form possesses either a comparable composition or concentration of active pharmaceutical ingredient relative to the existing product.
- The analytical method(s) are the same or very similar to the methods that are already in use.
- The method validation package encompasses the new methods.
- Personnel who developed the methods move from one site or laboratory to another as the project evolves.
- The new methods involve changes that do not substantially alter the ability to use the method (e.g., changes in sample preparation procedures or changes in calculation formulas).

Required elements of an analytical method transfer

This section presents the various components necessary to complete a successful method transfer by means of the comparative testing route. As will be discussed, many of the factors necessary for a compliant transfer are interrelated.

Preapproved test plan/SOP/protocol. Before implementing any

method transfer, one should set in place an approved document that describes both the general transfer process as well as the specific acceptance criteria necessary for the method(s) being transferred. Usually, both the R&D and quality units have general standard operating procedures (SOPs) that govern the transfer process. These SOPs describe the details of a method transfer protocol or test plan that is specific to the product and methods. This document should define clearly the responsibilities of both the transferring and receiving laboratories. It also should list all methods that will be transferred. A rationale for any methods not included (i.e., a transfer waiver) also must be provided.

The selection of materials and samples to be used in the method transfer should be described. In general, one does not choose GMP-released materials for transfer activities because the results of not meeting the predetermined acceptance criteria could trigger an out-of-specification (OOS) investigation. The identity and lot numbers of specific batches should be stated. If possible, certificates of analysis for all samples, including reference standards, should be supplied. All instrumentation and associated parameters should be described, including any disclaiming statements that may affect the outcome of the transfer. An example of the factors affecting method transfers have been described in a classic article by Kirschbaum (3). If possible, the instrumentation should be held constant during the transfer, thereby eliminating one variable from the process. Alternatively, it is recommended that the transferring laboratory consider running the method on instrumentation common to the quality unit before formal transfer.

Description of methods/test procedures. It is important to include records of all methods used during the transfer. Any validation data that are available should be given to the receiving laboratory. One should include any idiosyncrasies present in the method. A difficult method is not necessarily nonrugged. Rather, a thoroughly developed method will include the steps that must be followed and any pitfalls that may be encountered. In all procedures, step-by-step directions should be provided, including tips and tricks, safety considerations, and clear equations and calculations.

Description of test requirements. As part of the specific transfer, the number of lots, replicates, and injections (in the case of high-performance liquid chromatography) should be presented expressly. In the case of dissolution transfers, the number of individual dosage form units that will be tested should be stipulated. One should spell out such details so that small differences in the everyday analytical philosophies do not disturb the transfer process.

Rationale for test requirements. One should provide a rationale for the parameters chosen and their effect on the overall success of the transfer. This description also should explain any system-suitability parameters that already had been established for the method.

Acceptance criteria. The transfer protocol or test plan should include suitable acceptance criteria relevant to the tests and specific dosage forms. Giving hard and fast specifications for such criteria is not possible because a considerable number of exceptions would surely exist. At the recent PhRMA ARDSC work-

shop about method transfer, participants described a variety of approaches. Table I summarizes some of the responses to questions about acceptance criteria for analytical methods. The table clearly shows that the discrete acceptance criteria vary considerably from company to company. It also shows, however, that having systems in place to challenge the performance of a method during transfer is common during the transfer process.

Documentation of results. The results of the transfer should be documented in a report that summarizes all experiments and results. One should pay considerable attention to detail with respect to any and all aspects, observations, and experimental results. In some cases, results from the receiving laboratory may not meet the established acceptance criteria. Such situations should be addressed by a policy that describes how failure to meet predetermined acceptance criteria should be handled and how the overall transfer should be affected. PhRMA workshop attendees almost were unanimous in stating that failure to meet predetermined acceptance criteria does not constitute an OOS investigation. Regardless of whether such policy is followed, an investigation into all results that fail to meet the predetermined

Table I: Select acceptance criteria for assay methods per PhRMA ARDSC attendees September 2000 (2).

Question	Response
Do you perform linearity upon transfer?	Yes and no
How many lots for transfer?	2–3 covalidation and 1 other lot Bracket high and low strengths, if applicable
How many repetitive analyses?	1–6 depending on percent relative standard deviation
How many analysts at the receiving site?	1–2, some with same analyst but different equipment, day, etc.
Do you spike samples for impurities?	Yes and no (even split)

acceptance criteria should be performed and documented in the resulting summary report.

Use of statistics in data evaluation

Comparative testing as a means by which analytical test methods and procedures are transferred from one laboratory to another involves the generation of data that can be compared using one or more statistical tools. Although one certainly can evaluate the data subjectively, the use of statistics will build objectivity into the data analysis and allow unbiased comparison of the data sets. Because comparative testing involves destructive testing of individual samples, the strength of the transfer involves proving mathematically that the data sets are equivalent. Many transfers are governed by the statistics of the standard Student *t*-test (4). The *t*-test is useful for determining equivalence of like data sets and is generally sufficient for analyzing data results for comparative testing. A consensus of PhRMA workshop attendees held that both statistical and non-statistical approaches to data evaluation are acceptable. However, the decision whether to use statistics must be part of the test plan. It is not acceptable to use only mathematics as a means to explain a failed transfer.

Summary

The important aspects of the analytical transfer process as they relate to compliance, analytical data, and documentation have been discussed in this AAP. This AAP provides guidance for the performance of method transfer activities that meet regulatory requirements.

References

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4. P.C. Meier and R.E. Zund, *Statistical Methods in Analytical Chemistry*, (John Wiley & Sons, New York, NY, 1993). **PT**