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Analytical Method Transfer for Solid Dosage Forms

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ABSTRACT

The transfer of analytical procedure (TAP), also referred to as method transfer, is the documented process that qualifies a laboratory (the receiving unit) to use an analytical test procedure that originated in another laboratory (the transferring unit), thus ensuring that the receiving unit has the procedural knowledge and ability to perform the transferred analytical procedure as intended. Method Transfer enables to adapt method to new facility or instrument and to meet new facility validation requirements and also helps to maintain validated state of method. It gives documented guidance in principle and provides general recommendations on the necessary activities that should be addressed to conduct a successful intra- or inter- site transfer. It applies to all dosage forms such as sterile products, metered-dose aerosols and clinical trial supplies. There are many approaches to Method Transfer such as Comparative Testing, Co-validation between two laboratories, Revalidation, Transfer waiver.

Keywords: Method Transfer, transferring unit, receiving unit, validation.

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INTRODUCTION

Testing of pharmaceutical ingredient, in-process intermediate or finished product is critical for establishing the quality of the final pharmaceutical product. The transfer of analytical procedure, also referred as method transfer is the documented process that qualifies a laboratory (the receiving unit) to use an analytical procedure that originates in the other laboratory (the transferring or transferring unit), thus the receiving unit has the procedure, knowledge and ability to perform the transferred analytical procedure as intended.¹

Method transfer is closely related to validation but it is far more challenging because multiple laboratories and companies are involved. Hence method validation has to be carried out before implementing method transfer.

The goal of analytical method transfer is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement.²

The transfer of analytical procedure (TAP), also referred to as method transfer, is the documented process that qualifies a laboratory (the receiving unit) to use an analytical test procedure that originated in another laboratory (the transferring unit), thus ensuring that the receiving unit has the procedural knowledge and ability to perform the transferred analytical procedure as intended.³

Advantages of Method Transfer

- Gives the analyst complete knowledge of the method transferred.
- Method can be put to commercial use.
- Demonstrates the accuracy of method.
- Qualifies the laboratory to use a method that originated in another laboratory.
- If there are any critical issues occurring while conducting method transfer then they can be highlighted.
- It is a means to provide documented evidence of transfer of analytical procedure.⁴

Types of Transfers of Analytical Procedures

Analytical Method Transfer can be performed and demonstrated by several approaches. The most common is comparative testing performed on homogeneous lots of the target material from standard production batches or samples intentionally prepared for the test (e.g., by spiking relevant accurate amounts of known impurities into samples). Other approaches include co

validation between laboratories, the complete or partial validation of the analytical procedures by the receiving unit, and the transfer waiver, which is an appropriately justified omission of the transfer process. The test that will be transferred, the extent of the transfer activities, and the implementation strategy should be based on a risk analysis that considers the previous experience and knowledge of the receiving unit, the complexity and specifications of the product, and the procedure.

Comparative testing

Comparative testing requires the analysis of a predetermined number of samples of the same lot by both the transferring and the receiving units. Other approaches may be valid, e.g., if the receiving unit meets the predetermined acceptance criterion for the recovery of an impurity in a spiked product. Such analysis is based on a preapproved transfer protocol that stipulates the details of the procedure, the samples that will be used, and the predetermined acceptance criteria, including acceptance variability. Meeting the predetermined acceptance criteria is necessary to assure that the receiving unit is qualified to run the procedure.

Co-validation between two or more laboratories

The laboratory that performs the validation of an analytical procedure is qualified to run the procedure. The transferring unit can involve the receiving unit in an inter laboratory co-validation, including them as a part of the validation team at the transferring unit and thereby obtaining data for the assessment of reproducibility. This assessment is made using a preapproved transfer or validation protocol that provides the details of the procedure, the samples to be used, and the predetermined acceptance criteria.

Validation Approach

Performing AMT is not feasible due to the following (but not limited to):

- ✓ Less stable molecule or drug product/ drug substance being too sensitive to be transported.
- ✓ Drug product/drug substance being a narcotic/psychotropic substance; hence, legal complications in transporting the same.
- ✓ Considerable difference in the technical characteristics of test equipment available at RU as compared to that of SU.

Whenever 'Partial Validation' is being used as an alternate for Analytical Method Transfer, the following minimum parameters are included:

- Accuracy
- Linearity

- Specificity
- Method Precision
- Confirmation of LOD & LOQ of impurities/solvents
- Confirmation of RT/RRT of impurities/solvents

Transfer waiver

The conventional TAP may be omitted under certain circumstances. In such instances, the receiving unit is considered to be qualified to use the analytical test procedures without comparison and generation of interlaboratory comparative data. The following examples give the scenarios that may justify the waiver of TAP.

- The new products composition is comparable to that of an existing product and/ or the concentration of an active ingredient is similar to that of an existing product and is analysed by procedures with which the receiving unit already has experience.
- The analytical procedure being transferred is described in the USP-NF, and is unchanged.
- The analytical procedure transferred is the same as or very similar to the procedure already in use.
- The personnel in charge of the development validation, or routine analysis of the product at the transferring unit are moved to the receiving unit.

If eligible for transfer waiver, the receiving unit should document it with appropriate justifications.⁵

REQUIRED ELEMENTS OF ANALYTICAL METHOD TRANSFER^[6,7]

This section presents the various components necessary to complete a successful method transfer by means of the comparative testing route.

Preapproved Test Plan/SOP/Protocol

Before implementing any method transfer, an approved document that describes both the general transfer process as well as the specific acceptance criteria necessary for the method(s) being transferred is set. 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 or intended execution strategy that is specific to the product and methods. The protocol contain the following topics: objective, scope, responsibilities of transferring and receiving units, materials and instruments that will be used, analytical procedure, experimental design, and acceptance criteria for all the tests and/or methods included in the transfer. A

rationale for any methods not included (i.e., a transfer waiver) are provided. GMP-released materials are used 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 are stated. Certificates of analysis for all samples, including reference standards, are supplied. All instrumentation and associated parameters are described, including any disclaiming statements that affect the outcome of the transfer. If possible, the instrumentation is held constant during the transfer, thereby eliminating one variable from the process. The transferring laboratory runs the method on instrumentation common to the quality unit before formal transfer.

The documentation section of the transfer protocol includes report forms to ensure consistent recording of results and to improve consistency between laboratories. This section contains the additional information that is included with the results, such as example chromatograms and spectra, along with additional information in case of a deviation. The protocol also explains how any deviation from the acceptance criteria is managed. Any changes to the transfer protocol following failure of an acceptance criterion are approved before collection of additional data and documented.

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) are presented expressly. In the case of dissolution transfers, the number of individual dosage form units are tested as well as stipulated.

The expired, aged, or spiked samples are carefully chosen and evaluated to identify potential problems related to differences in sample preparation equipment and the impact of potential aberrant results on marketed products.

Rationale for test requirements

A rationale for the parameters chosen and their effect on the overall success of the transfer are provided. This description explains any system-suitability parameters that had been established for the method.

Acceptance criteria

The transfer protocol or test plan includes 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 exists. Acceptance criteria vary from company to company.

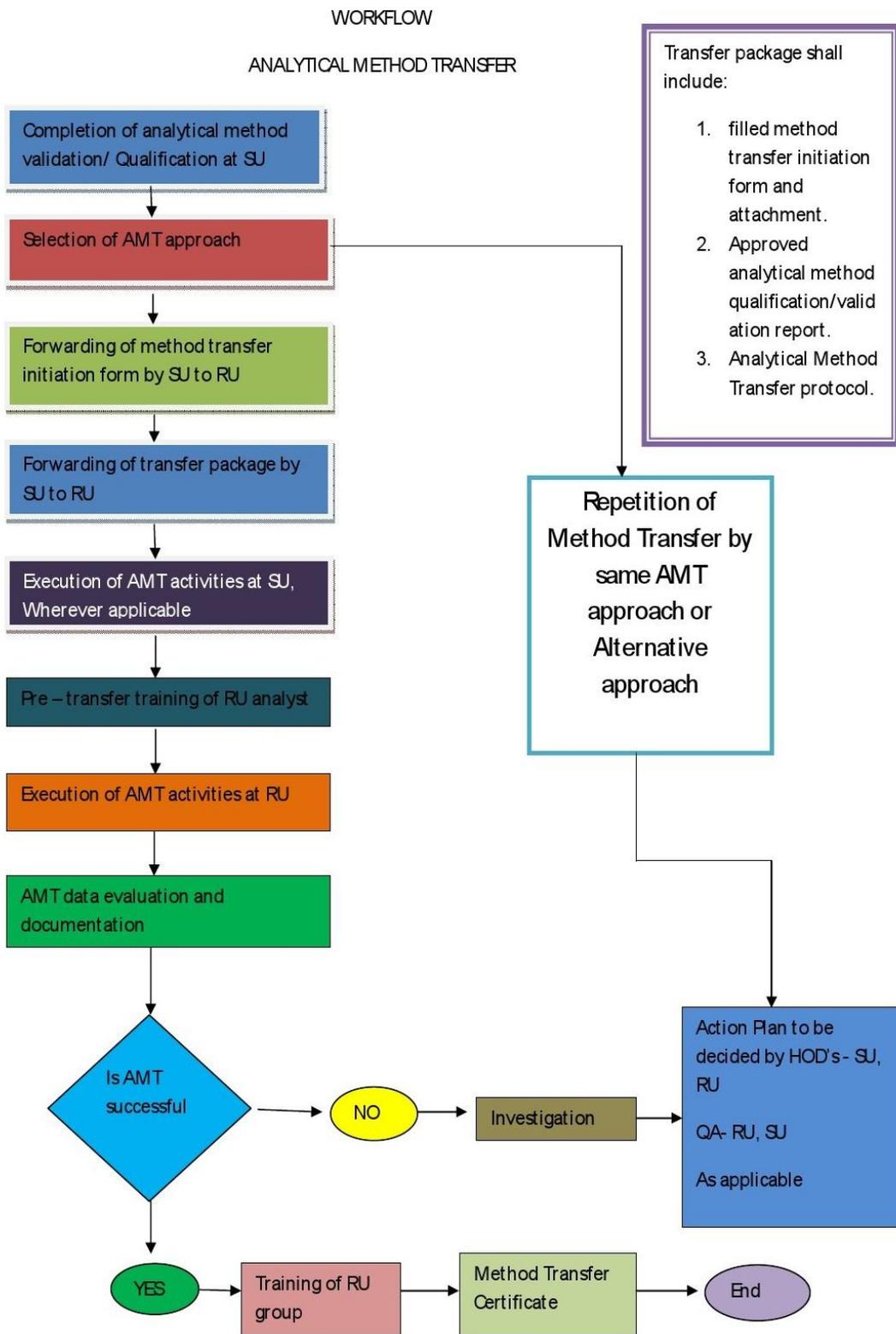
The transfer acceptance criteria, which are based on method performance and historical data from stability and release results, include the comparability criteria for results from all study sites. These criteria is derived using statistical principles based on the difference between mean values and established ranges and is accompanied by an estimation of the variability (e.g., percent relative standard deviation [%RSD] for each site), particularly for the intermediate precision % RSD of the receiving unit and/ or a statistical method for the comparison of the means for assay and content uniformity tests. In instances of impurity testing, where precision may be poorer such as in case of trace impurities, a simple descriptive approach is used. Dissolution is evaluated by a comparison of the dissolution profiles using the similarity factor f_2 , or by comparison of data at the specified time points.²⁶

The Analytical Procedure

The procedure is written with sufficient detail and explicit instruction, so that a trained analyst can perform it without difficulty. A pre-transfer meeting between the transferring and receiving unit helps to clarify any issues and answer any questions regarding the transfer process. The complete or partial validation data is made available to the receiving unit, along with any technical details required to perform the test. A difficult method is rugged. Rather, a thoroughly developed method includes the steps that must be followed and any pitfalls that may be encountered. In all procedures, step-by-step directions are provided, including tips and tricks, safety considerations, and clear equations and calculations.

Transfer Report

When the TAP/AMT is successfully completed, the receiving unit prepares a transfer report that describes the results obtained in relation to the acceptance criteria, along with conclusions that confirm that the receiving unit is now qualified to run the procedure. Any deviations are thoroughly documented and justified. If the acceptance criteria are met, the TAP is successful and the receiving unit is qualified to run the procedure. Otherwise, the procedure cannot be considered transferred until effective remedial steps are adopted in order to meet the acceptance criteria. An investigation conducted provides guidance about the nature and extent of the remedial steps, which varies from further training and clarification to more complex approaches, depending on the particular procedure.²⁷



PROCESS OF ANALYTICAL METHOD TRANSFER

Once Analytical Method Validation is completed successfully Analytical Development Laboratory identifies the need for Method Transfer based on the requirements.

Method Transfer Initiation Form is forwarded by the Analytical Development Laboratory which is called as Transferring Unit with the details of requirements.

- List of methods to be transferred
- List of instruments/equipments, working standards, reference standards used.
- List of reagents

On receiving Initiation form, the receiving unit checks for the availability of requirements and takes decision about acceptance or rejection of method transfer initiation form.

There are two possibilities:

- In case of acceptance of initiation form, receiving unit fills the form and send it to the transferring unit.
- In case of non acceptance, the reason is stated along with the alternate plan.

Upon acceptance, Transferring unit forwards the following documents to Receiving unit:

- Method Transfer Initiation form
- Method Transfer Protocol
- Analytical Method Validation Report

Analytical Method Transfer is conducted at the receiving unit using any of the method mentioned below:

- Comparative testing
- Co-validation between two laboratories
- Validation approach

Any deviation during method transfer from preapproved protocol must be documented. Deviation report must be filed and Analytical method validation data must be reviewed. In case of any changes, change control form is filled and circulated in all the departments (Research and development, Quality Assurance, Planning and Development) to ensure that the changes would not affect any parameters of formulation.

Table 1 Number of batches used for method transfer

Sr. No.	Type of Product	Minimum Batches [#]	Number of
1.	API	Two	
2.	Drug product- single strength	Two	
3.	Drug product- two or more than two strengths*	One batch each- strength and highest strength	Lowest

CONCLUSION

Method Transfer enables a laboratory to use the procedure evolved in another laboratory. The transfer of method depends on the complexity and criticality of method and regulatory requirements. Method transfer demonstrates the accuracy of the method. The criteria for transfer of method are based on the standard operating procedure of the test method and also on the validation data of method. Method Transfer is successful when the results are within the acceptable limits. The method transfer data is documented and documents are maintained in the receiving unit.

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