Analytical Method Technology Transfer From Quality Control Laboratory To Manufacture Area

Linnette Pérez Dominicci
Master in Manufacturing Competitiveness
Rafael Nieves, Pharm. D
Industrial and Systems Engineering Department
Polytechnic University of Puerto Rico

Abstract *— The project was developed with the intent to document the analytical transfer method to reduce in-process concentration testing cycle time. A reduction of up to 50% turnaround time (TAT) downtime was achieved. Waste reduction due to no sample preparation, gowning cost reduction, since there is no need for the operators to take the sample to the Quality Control (QC) laboratory and transferring the in-process method to the manufacturing area allows more capability to the QC laboratory to perform another testing were other improvements obtained from the project.*

Technology method transfer tools were applied to generate a successful in process method transfer from the QC laboratories to the manufacturing area. The implementation of this project complying with all the standards required by the company and the different regulatory agencies will improve the capability and competitiveness of the manufacturing area among the company sites.

Key Terms *— Analytical Method Transfer, Manufacturing Process, Protein Concentration, Turnaround time (TAT) reduction.*

PROBLEM STATEMENT

In these times that the manufacturing industry is extremely competitive, moving amazingly fast, and where the waste of time must be minimized, alternatives of manufacturing a product with the leanest process is a topic that is being studied. To have a product release to the market as quickly as possible, complying with all the standards required by the different regulatory agencies, improvements to the process to made them leaner needs to be tracked.

This been said, one of the downtimes during the manufacturing process is the in-process quality control tests. These tests are frequent analyses performed during the production, to ensure that established criteria or parameters are met before continuing with the process. These tests normally are performed by a certified Quality Control (QC) laboratory. Taking the in-process sample to the QC laboratory, performing a test, and waiting for results it is considered as downtime. This is also considered as "waste" on any lean manufacturing process. Therefore, transferring a new in-process methodology that can be used by an operator in the manufacturing suite will reduce the downtime, which allows having a leaner manufacturing process.

Research Objectives

The objective of this research is to reduce the downtime at a 50% of the manufacturing turnaround time (TAT) for the concentration determination of in-process testing, by the transfer of a new concentration determination in-process testing methodology from the QC laboratory to the manufacturing area.

Research Contributions

Normally, the QC laboratory turnaround time (TAT) for the concentration determination of in-process testing is approximately 4 hours. This type of testing requires sample preparation, equipment calibration, testing execution, documentation, data verification, reporting, and results sample approval.

The contributions of this research are the following:

- Waste reduction due to no sample preparation is needed with the new in-process methodology.
- New method has less variability than the current one.
- Reduce to 50% (2 hours) the waiting time downtime.
- Gowning miscellaneous cost reduction, since there is no need for the operators to take the sample to the QC laboratory.
- Provides more capability to the QC laboratory to perform another testing.

LITERATURE REVIEW

In a constantly changing world where globalization, a process in which businesses start operating on an international scale, has become a common practice the Technology transfer process occurs more often. Analytical method transfer is a fundamental part of any Technology transfer activities. Saying this, we must understand and know the answers to the following questions:

- What is an analytical method transfer?
- Why does an analytical method transfer need to be done?
- How many types of analytical method transfer exist?
- What are the parts of the analytical method transfer?

After seeking through several regulatory agencies guidance documentation, this activity is a much-discussed topic in the current Good Manufacturing Practices (cGMP) regulated sector. Agencies such as Food and Drug Administration (FDA), World Health Organization (WHO) among others, seek the assurance of a well-documented, and sustainable transfer of analytical procedures [1]. Therefore, most of the pharmaceutical companies do not take lightly this type of activity and have in place the standard operating procedures to successfully achieve it.

What is an Analytical Method Transfer?

According to United States Pharmacopeia (USP), Chapter ⟨1224⟩, Transfer of Analytical Procedures [2], "transfer of analytical procedures (TAP), also referred to as method transfer, is the documented process that qualifies a laboratory (the receiving unit) to use an analytical test procedure". This transfer is performed in conjunction with a transferring area that ensures that the receiving area is qualified and can execute the analytical method transferred.

Why does an Analytical Method Transfer need to be Done?

Transfer of any type of analytical method is required by the regulatory agencies. It is done as part of the sustainability of the product. Once the analytical method is validated, it is shared as needed through a documented process to an appropriate accountable and certified area.

It is done also as part of a pharmaceutical company's business strategies due to the need for additional capacity, operations relocation or consolidations, and mergers.

Analytical method transfer is normally performed generating a transfer protocol, which contains parameters to be evaluated and acceptance criteria that will be applied to the results generated by the receiving area. After protocol execution is completed, a transfer report is generated to compile and document the activity in question.

How many Analytical Method Transfer Types Exist?

Based on the General Chapter ⟨1224⟩ of the USP [2], there are four analytical method transfer types:

- Comparative Testing, which normally involves the analysis of a predetermined number of samples of the same lot by both the transferring and the receiving area. This is the most common approach.
- Co-validation between two or more laboratories or areas, in this case, both the

transferring and the receiving area participate as part of the analytical method validation.

- Revalidation, which involved the execution of a partial activity where both areas participate as part of transfer activities.
- Transfer Waiver, in this case, an analytical method transfer can be omitted under the following circumstances.
    - When the product composition is equal or comparable to an existing product that is already analyzed by the receiving area.
    - The analytical testing is described in a compendial methodology, (USP, European Pharmacopeia, Japanese Pharmacopeia among others).
    - The analytical method is the same as or similar to a method already in use in the receiving area.
    - The personnel that perform the analysis at the transferring area is relocated to the receiving area.

What are the Parts of the Analytical Method Transfer?

According to WHO, Annex 7, guidelines on transfer of technology in pharmaceutical manufacturing [3] to achieve a successful analytical method transfer, coordination, and planification of several activities need to occur. The following general principles and requirements should be met:

- An Analytical Master Transfer Plan (AMTP) must include the quality aspects of the project and be built upon the standards of quality risk management approach. This plan must define the transfer strategies, such as roles and responsibilities, transfer elements (sample type, acceptance criteria), significance tests (accuracy and precision), training requirements, and documentation (transfer protocol and report) that need to be generated in order to support the transfer activities.
- The capabilities of the receiving area should be similar to the transferring area and facilities and equipment should operate according to similar operating principles. A technical gap assessment between both areas (transferring and receiving) including risk assessment and potential regulatory gaps, should be performed.
- Knowledge transfer to the receiving personnel must be facilitated. Familiarization runs are normally encouraged or training at the transferring area is highly recommended.
- When transferring to another country or region, requirements from regulatory agencies of both transferring and receiving areas should be considered and interpreted consistently throughout any transfer program project.

Any lack of transparency can cause having an ineffective analytical method transfer process. This activity must be a well-document one, where all elements aforementioned are synchronized to ensure having a receiving area capable of generated reproducible and accurate results that complies the requirements of the company and regulatory agencies.

METHODOLOGY

The purpose of this research is to describe the tools to be used to transfer a new in-process methodology from transferring to a receiving area. It is well understood that any analytical methods transfer can be audited by regulatory agencies, to ensure that procedures were followed by both areas during this process. It is clear, that there are some challenges during a transfer of an analytical method and that it can be very time consuming and stressful. Planning tools need to be used to avoid delays in this process. Although pharmaceutical companies have standard operational procedures (SOP) in place to be followed, these do not contemplate how long it will take and what tools should be used to ensure a flawless transfer.

According to the article “The transfer of analytical procedures” written in the Journal of Pharmaceutical and Biomedical Analysis [4], the key to accomplishing successful analytical method transfers is to have an opened communication among the transferring and receiving areas. This should be enabled by written communication, SOP,

flow charts, clear definition of roles and responsibilities, what are the type of transfer categories, technical documents such as the transfer plan and report. Another element important to mention is what will be the strategies in case of failed transfer. Potential drawbacks must define such that they can be escalated on time.

The transfer activities target is to prove the receiving area's ability to execute the analytical methods transferred effectively. According to the article mentioned above, "it has to be pointed out that the performance and ability of a receiving area is always the sum of the ability of the staff and the performance characteristics of their equipment and should not depend on the properties or quality of the samples" [4].

Therefore, this discussion will consist in defining what should be the strategy and the methodology to be followed to have a thriving and on-time analytical method transfer.

Analytical Method Transfer Planification and Execution

The transfer of an analytical method can happen in different ways and circumstances: from transferring only a method to a whole product specification test requirement, which contains several test methods. For this project, the transfer of a single method will be considered. Nonetheless, the transfer approach process will remain the same. Figure 1 contains the process flowchart of an analytical method transfer. To ensure a flawless activity, these nine (9) steps process should be taken into consideration and will be discussed as part of the transfer methodology.

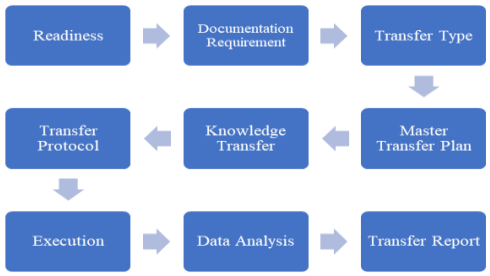

Figure 1
Analytical Method Transfer Planning Process Flowchart

Readiness

For the success of an analytical method transfer, an open and reliable communication between transfer and receiving areas is crucial. A full risk assessment should be performed, taking into consideration the receiving area capability. Once it is understood, timelines, roles, and responsibilities need to define and agree on. Having all the key elements in place, such as the method to be transferred is valid and fit for use, equipment required to perform the tests are qualified and fulfill in compliance with regulatory and company requirements, planification for transfer activities can be set. Face to face meetings is crucial, and these should be scheduled at least once a week. The frequency of these meetings can change according to the transfer activity's necessity.

A project manager can be hired to track the transfer activities, or a timeline tracking tools can be used, managed by either area. Normally is the transferring area that performs this task. Nonetheless, it will depend on the necessity of the areas to complete the task. Roles and responsibilities will be discussed further on.

Required Documentation

Written documentations are one of the most important parts of any analytical method transfer. It is where the transfer activities are perpetuated and are used for future reference in case a doubt roused, and/or troubleshooting is needed. As well, these documentations can be audited by any regulatory agencies.

Before the start of an analytical method transfer, documents listed in Table 1 needs to be shared with the receiving area. Some companies call this the transfer documentation package. Before starting any validation, activity these are shared, to ensure that the receiving area gains all the knowledge needed ahead of time. Table 1 also summarized the documentation required as part of the transfer activities; nonetheless, additional documentation can be generated, according to the company's procedure.

Table 1

Required Documents as Part of Transfer Method Activities

Prior Transfer	Generated during Transfer
Method validation protocol	Risk Assessment
Equipment qualification protocol/report	Gap analysis
Method specifications	Master Transfer Plan
Sample handling and storage	Transfer Protocol
Change controls documentation	Transfer Report
Procedures	
Test reporting forms	
Training requirements	

Transfer Types

USP General Chapter ⟨1224⟩ [2] describes the general requirements to be followed as part of the transfer process. Table 2 contains four (4) types of analytical transfer that are recognized. One of these or a combination can be used as part of method transfer activities.

Table 2

USP General Chapter ⟨1224⟩ Types of Analytical Transfer

Comparative testing
Co-validation
Complete or partial (re-)validation
Transfer waiver

Master Transfer Plan

Normally the master transfer plan is where all the agreements are documented. It is established the transfer duration, what is needed, who will be responsible for what, transfer type, it is like and service agreement between transferring and receiving areas. Table 3 summarized Roles and responsibilities during an analytical method transfer; nonetheless, these can vary according to the company's procedure.

Knowledge Transfer

Making sure that the receiving area gains knowledge in the methodology can be achieved in many ways. Therefore, before starting any formal transfer activity, familiarization runs can be conducted in the receiving area. This task can avoid potential drawbacks. Another way to achieve the knowledge transfer is that the chosen person can travel to the transferring area and be trained by the technical subject matter experts. This agreement can be established as part of the master transfer plan.

Table 3

Roles and Responsibilities during an Analytical Method Transfer

Transferring Area	Receiving Area
Provide training, if required	Identified the adequate personnel to be trained and execute the familiarization runs
Propose the methods transfer strategy, experimental design	Review analytical methods provided
Provide supporting documentation reports	Agree on acceptance criteria established
Provide equipment specification to used and standard reference samples	Ensure that the required equipment is available and qualified
Execute the transfer protocol	Execute the transfer protocol, provide reviewed data to the transferring area
Compile and approve transfer reports	Review and approve transfer reports

Transfer Protocol

The method transfer protocol is where is established the strategy of the activity. To ensure a successful transfer, it should be discussed before approval with the receiving area. This document must contain all aspects recommended in the company and appropriate regulatory guidelines and/or procedures. The experimental studies' strategy and acceptance criteria should be defined. For the sample acceptance criteria determination, the International Society of Pharmaceutical Engineering (ISPE) Guide [6] can be used. These criteria were established with involvement from regulatory authorities from the United States, United Kingdom, Canada, and Japan. Table 4 summarized transfer protocol sections; nonetheless, these can vary according to the company's procedure.

Table 4

Transfer Protocol Sections

Background
Equipment's to be used
Reagents/Material/Consumables
Transfer samples description
Procedure
Data Calculation
Acceptance criteria

Execution

After approving the transfer protocol and having both areas participants trained in the strategy, only the execution of the document remains. Being this one a critical part of the transfer activity. Any deviation of the approved protocol must be addressed and documented. After performing and reporting the tests described in the transfer protocol, results must be verified and approved by the corresponding personnel. Once the data is verified and results are approved, these should be shared with the responsible area that will generate the transfer report.

Transfer Report

Once results from both areas are received, they are tabulated and evaluated against the transfer protocol acceptance criteria. Any deviation should be documented as part of the transfer report. The document will summary all activities performed and should determine the effectiveness of the execution. It should conclude if the receiving area is qualified to execute the method in question. Table 5 summarized transfer report sections; nonetheless, these can vary according to the company's procedure.

Table 5
Transfer Report Sections

Background
Tabulated Results of both areas
Results Evaluation
Clear conclusion
Deviation or discrepancies, if applicable
Attachments (e.g., raw data, analytical reports)

These nine (9) steps process is key and must be followed to have a successful analytical method transfer. It is important to mention that each step that was taken into consideration will allow companies expand operations and feel confident of the quality of their product.

RESULTS AND DISCUSSION

The purpose of this section is to document the activities performed as part of the analytical transfer method process of the in-process concentration testing from the QC Laboratories to the manufacturing area. Figure 2 shows the current process of the in-process concentration testing flow at the QC Laboratory.

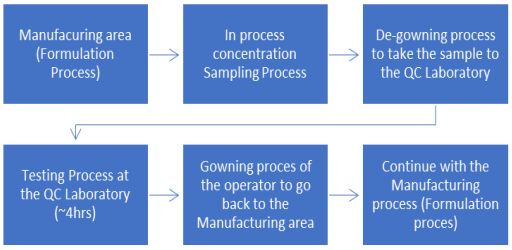

Figure 2
In-process Concentration Testing Flow at the QC Laboratory

Formulation process of the drug product is start in the manufacturing area. To achieve the desired protein concentration at the 85% of the formulation process, an in-process concentration sample is collected and needs to be deliver to the QC Laboratory. An Operator needs to de-gown to take the sample to the QC Laboratory. Sample needs to be received in a logbook by a QC Analyst. To enter to the manufacturing area a continue supporting the formulation process, the Operator needs to gown again. The QC Laboratory takes approximately four (4) hours to provide an approved concentration result of the in-process sample. Then the manufacturing area uses this value to calculate the remains buffer needed to achieve the 100% concentration formulation process.

To reduce at 50% the downtime of waiting of the QC Laboratory results, analytical transfer method process of the in-process concentration testing from the QC Laboratories to the manufacturing area was proposed. To ensure a flawless transfer activity, the nine (9) steps process were consolidated into three (3) main activities and were taken into consideration as part of the transfer methodology.

- **Master Transfer Plan**
  - Readiness (documentation requirements, and knowledge transfer).
  - Roles and Responsibilities.
  - Qualification Philosophy.

- **Analytical Transfer Method Protocol**
  - **E**xecution and data analysis.
- **Analytical Transfer Method Report**
  - Documentation of the transfer activities
  - Each of these steps are further discussed is this section.

Master Transfer Plan

This master transfer plan is to provide the basic and organizational structure for the execution of the analytical transfer method process of the in-process concentration testing from the QC Laboratories to the manufacturing area.

Readiness Process

In order to have a successful method transfer process, readiness is a fundamental key element. Table 6 summarized the readiness process that need to happen prior to start a method transfer.

Table 6
Readiness Process Element Prior to Start a Method Transfer

Documentation	Material	Knowledge Transfer
Protocol/Report	Equipment	Familiarization Run
SOP (New and/or Change)	Reagents	
Method/Form	Consumables	On the Job execution
On the Job generation		

Roles and Responsibilities

Having the roles and responsibilities established at part of the method transfer will help to ensure task are completed. Table 7 establish who is responsible of what.

Table 7
Manufacturing and QC Laboratory Transfer Plan RACI Chart

Activities /Task	Receiving Area (Manufacturing)	Project Manager	Transferring Area (QC Lab.)	Quality Assurance
Overall Project Accountability for transfer	C	A/R	I	I
Generate Instrument Procedure SOP	C	A/R	C	C
Review and Approval of SOP	R	A/R	C	R
Purchase of Equipment as needed	A/R	C	C	N/A
Provide Tech Transfer Samples	C	A/R	C	N/A
Generation of Training Documentation	C	A/R	C	C
Execution of Training	R	A/R	R	N/A
Execute Shake-Down Analysis	R	A/R	R	N/A
Generate Protocol	C	A/R	C	C
Review and approval of Protocols	R	A/R	C	R
Execution of Experiments	R	A	R	N/A
Review of Raw Data Packets	C	R	A/R	C
Generate Report	C	A/R	C	C
Review and approval of Reports	R	A/R	C	R
Provide support if any investigation occurs	R	A/R	R	R
Review and approval any investigation, if applicable	R	A/R	R	R

R = Responsible: Individuals or groups who perform an activity/task.

A = Accountable: The individual or group who is ultimately accountable for the completion of the activity/task.

C = Consulted: Individual(s) or group(s) who are to be consulted prior to completion of the activity/task or before the decision is made.

I = Informed: Individual(s) or group(s) who are to be informed of the completion of the activity/task, or of the decision result.

Qualification Philosophy

The type of transfer will let you know the amount of work that needs to be done. In addition, it will let you know what are the control are put in place, to ensure that the analytical method was transfer properly. Table 8 documents the Transfer type used and parameters that need to be tested to ensure the quality of the transfer.

Table 8
Transfer Type and Parameters

Transfer Type	Parameters to be Tested
Comparative Testing	System Suitability Repeatability Intermediate Precision

Analytical Transfer Method Protocol

In this transfer, method protocol, precision (repeatability, intermediate precision, and reproducibility), accuracy and system suitability were the parameters selected to measure the receiving area's ability to determine In-process protein concentration. Table 9 summarizes the transfer protocol parameters, objectives, and acceptance criteria.

Analytical Transfer Method Report

This report documents the Transfer activities results in-process protein concentration determination. Table 10 summarizes the in-process testing successful results from the analytical Transfer methodology from the QC Laboratories into the Manufacturing Areas.

Table 9

Technical Transfer Table

Parameter	Objective	Acceptance Criteria
Precision- Repeatability (Intra-assay) (receiving area)	To determine the precision under the same operating condition over a short interval of time.	% RSD of nine-determination sample concentration must be within ± 5.0%.
Precision-Intermediate-Precision (receiving area)	To determine if suitable precision is obtained when performed by different associates on different days.	%RSD of concentration measurements of six associates on different days must be ≤ 5.0%
Precision-Reproducibility (Inter-area) (receiving and transferring area)	To evaluate the reproducibility of the method when the same samples are analyzed in the transferring and receiving areas.	The %RSD for reportable results for all associates from the receiving and transferring areas must be ≤5.0%.
Accuracy	To determine the closeness of agreement between the concentration obtained by the receiving area and transferring sample concentration.	The % difference between the averages of each associate reportable results in the receiving area compared to the transferring sample concentration for each lot must be ±5.0%.
System Suitability	To demonstrate that the method is performing as required producing valid results.	Only valid experiments (all system suitability criteria met) will be used in this technical transfer.

Table 10

Transfer Protocol Summary Results

Test	Acceptance Criteria	Results				Pass/Fail
Repeatability (Intra-assay) (receiving area)	The % RSD of nine (9)-determination sample concentration must be within ± 5.0%.	Associates	% RSD (%)			Pass
		1	0.3			
		2	0.4			
		3	0.3			
		4	0.2			
		5	0.4			
		6	0.3			
Intermediate-Precision (receiving area)	The %RSD of the combined protein concentration measurements of six (6) associates on different days must be ≤ 5.0%.	Sample Type	% RSD (%)			Pass
		In process	1.2			
Reproducibility (Inter-area) (receiving and transferring area)	The %RSD for reportable results for all associates from the receiving and transferring areas must be ≤5.0%.	Sample Type	% RSD (%)			Pass
		In process	1.1			
Accuracy	The % difference between the averages of each associate reportable results in the receiving area compared to the transferring sample concentration for each lot must be ±5.0%.	Associate	Percent Difference (%)			
			Rep. 1	Rep. 2	Rep. 3	
		1	1.0	0.1	0.3	Pass
		2	0.5	0.5	0.1	
		3	0.6	0.5	0.2	
		4	0.9	0.2	0.2	
		5	0.1	0.1	0.1	
		6	0.5	0.0	0.1	
System Suitability	The % difference between Standard measured concentration and standard COA must be within ± 5%	All System Suitability criteria during transfer were met.				Pass

CONCLUSIONS

The analytical method transfer activities for a new in-process methodology from the QC laboratory to the manufacturing area was successfully achieved. The purpose of this research topic was to describe the tools to be used to help reduce downtime in the manufacturing suite, making the process leaner. Therefore, contributions of this research were successfully achieved. Normally this type of method transfer activity is scheduled to be completed in 6 months. Nonetheless, by using these method transfer tools, this activity was completed one-month ahead schedule.

As shown in Figures 3 and 4, the in-process concentration testing cycle time was reduced from four (4) hours to two (2) hours.

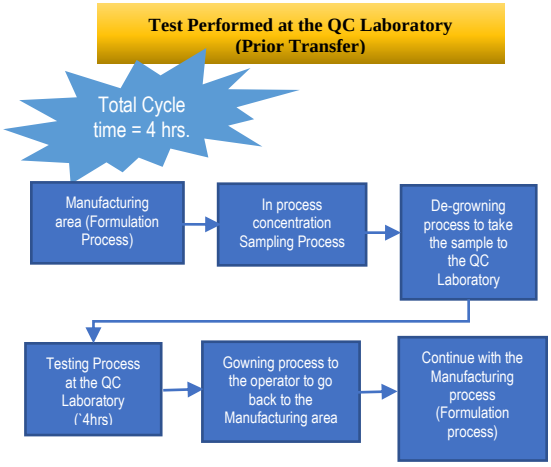

Figure 3
In-process Concentration Testing Cycle Time Prior Transfer

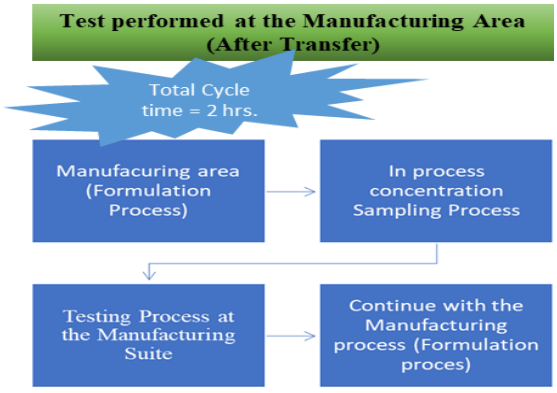

Figure 4
In-process Concentration Testing Reduction Cycle Time, After Transfer

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