**Analytical method transfers (AMTs)** are typically performed as a precursor to a critical step in the drug-development timeline, such as bringing on a new manufacturing facility, release testing of clinical or commercial material, or initiating stability studies at a quality-control laboratory. AMTs document that a new internal or external testing laboratory is qualified on the previously validated analytical method in order to generate current Good Manufacturing Practices (cGMP)-compliant data.

Not as straightforward as implied
The development of AMTs is neither easy nor simple. According to the U.S. Food and Drug Administration’s (FDA) Analytical Procedures and Methods Validation for Drugs and Biologics: Guidance for Industry, “…analytical procedures should be described in sufficient detail to allow a competent analyst to reproduce the necessary conditions and obtain results within the proposed acceptance criteria.”1 Although this statement implies that the process should be relatively straightforward, it does not mean AMTs are as simple as providing the analytical method to the new testing site and assuming it will be able to execute the method successfully. Differences in instrumentation, techniques, procedures and even interpretations of an analytical procedure can lead to preventable AMT failures. To ensure successful AMTs and avoid preventable failures, it is critical to develop a well-defined transfer plan with open lines of communication.

**The transfer process**
In any technology transfer (process) there are two primary parties involved: the “sending unit” (SU) and the “receiving unit” (RU). The SU, also known as the transferring laboratory, is the source or originating laboratory for the of the analytical procedure. The RU, also known as the receiving laboratory, is the internal or external laboratory being qualified on the analytical procedure.

While the process of analytical transfers between the SU and RU is typically thought of as straightforward, involving only two sites, the actual process over the lifetime of the analytical method can be very complex, as shown in Figure 1. In today’s environment, transfers can occur between multiple internal and/or external facilities, which may or may not involve the originating lab—the lab that developed and validated the method. For example, an analytical procedure may be developed and validated by a pharmaceutical company’s internal research and development (R&D) lab, then transferred internally to the company’s manufacturing site, and then later transferred to an external contract manufacturing organization (CMO) or contract research organization (CRO). This can occur over a period of months or years.

**Communication is key**
It is vital to understand that the AMT process should never be treated as a checkbox routine. Just because a method has been validated does not mean that the method will transfer. Some AMT failures do occur as the result of true method issues. However, the vast majority are preventable and often caused by miscommunication, misinterpretation of the information provided, or failure to share appropriate information on the method. Utilizing a defined process is the first step to ensure successful technology transfer and eliminate inadequate communication or lack of communication. An example of such a process is shown in Figure 2.

For successful execution of the transfer plan, both the SU and the RU have multiple responsibilities, as defined in Figure 3.

In preparation for the transfer, a critical first responsibility of the SU is to gather the information to be provided to the RU. This information will be part of the Transfer Package and should contain the following: analytical data; previous method validation reports—how did it perform under validation; what kind of robustness criteria?; previous transfer reports—how well have transfers occurred in the past?; relevant standard operating procedures (SOPs), including techniques that are defined by SOPs and may not be outlined in the analytical methods; general data, including example chromatograms and trends—how has the method performed over time?; quality-control (QC)/stability data—how is it performing on a day-to-day basis); and a list of previously encountered issues and how these were resolved.2

To guide transfer activities, it is important to establish communication protocols. These will include:

* Conducting pre-transfer meeting(s) between the SU and RU to work out details and answer questions;
* Establishing single points of contact for both the SU and RU; and
* Establishing cadence for updates (i.e., weekly/bi-weekly meetings).

**Key items in site evaluation**
One of the key steps is a RU site evaluation to ensure that the RU has the resources and experience to perform the transfers and to evaluate any potential differences between the sites:

* Equipment

- Are there differences between brands/models of instruments?
- Are instruments maintained similarly between sites?

* Lab infrastructure/environmental conditions

- Direct/indirect sunlight
- Lighting sources/types
- Temperature and humidity controls

* Laboratory reagent sources

- Which vendors/grades are used?

* Analyst training

- How are they trained on the analytical technique?
- Paper training vs hands-on training

**Types of testing**
As defined in USP 1224, there are many acceptable approaches to accomplish an analytical method transfer.3 Several factors should be evaluated when determining which type of transfer is appropriate for the product/situation:

* Timing
* Cost
* Logistics
* Instrumentation/method changes
* Compendia

When performing this evaluation, it is important to note that some of these factors can have negative impacts on the other factors. For example, designing an AMT to perform the transfer in the shortest time frame may not be the most cost-effective manner. It is therefore important to understand key drivers for the transfer and potential impacts of a proposed transfer approach.3
 **Comparative testing**
The most common method for AMT is comparative testing. As defined in USP 1224, comparative testing requires the analysis of the same set of samples by both the SU and the RU.4
Choosing the correct, or appropriate, samples can be critical to ensure a successful transfer. Utilizing multiple lots if available is recommended; relying on a single lot may be risky, especially if there is some lot-to-lot variability observed and/or the process involves a drug product method. For impurity methods, ensure that the samples contain the impurities detailed in the method; if the samples do not, the use of aged/expired samples, spiked samples or forced degraded samples is highly recommended. Clinical trial material that is actively being used and commercial material on the market should not be used in the transfer.

**Co-validation or multisite validation**
With the co-validation or multisite approach, the RU executes some aspects of method validation. This typically involves reproducibility testing in conjunction with the SU. Although this can be an efficient way to transfer the method, it can lead to delays in finalizing the validation report. If, for example, failures are encountered by the RU during its portion of the testing, validation will be delayed until all transfer issues are resolved.

**Revalidation**
Revalidation or partial revalidation is also considered acceptable for AMTs. It is commonly performed when the SU is unable to participate in the transfer activities. This process generally requires more time and is more expensive compared with the other modes of transfer. As part of the process to demonstrate that it is qualified, the RU performs a subset of the original validation. Typical parameters may include:

* Accuracy
* Precision
* Linearity
* Robustness

Revalidation may also be required in case of a method change. For example, the SU may use a different brand or model of instrument than the RU. In this case, revalidation may be required to demonstrate that the method is not only transferred, but that it is also validated on the new instrument.5

**Waiver**
In a limited number of cases, AMTs may be omitted. One example would be methodologies in which the presence of the sample does not impact the analytical technique and the RU already has documented experience on that technique (e.g., pH, loss on drying, melting point, etc.). A justification should always be prepared detailing the reasons why this approach is appropriate.

**Training**
Proper training is another prerequisite for AMT success. Generally, three types of training methods are used during AMTs:

* Remote. This is the simplest and most commonly used training process. The RU trains solely based on the information provided in the transfer package. However, remote training is also the source of most preventable failures.
* Onsite. In this case, the SU trains the RU onsite (at either the SU or RU lab). This method is generally preferred for biotechnology companies and/or in case of complex AMTs. It is costlier and more time-consuming than remote training, but it generally leads to relatively few transfer issues.
* Dual onsite. This training process is the most complex and is typically used only for extremely complex methods. It has a very low failure rate, but it is very time consuming.

  -The RU sends its analysts to train at the SU laboratory and to generate data with the SU.
  -The RU analyst and the trainer from the SU then travel to the RU to generate data at the RU.

**Data evaluation and transfer report**
The final steps of a successful transfer are to evaluate the transfer data against the pre-established acceptance criteria and to prepare the transfer report. While it is more common for the SU to write the transfer report, it is perfectly acceptable for the RU to do it. This report should include the results, as well as any discrepancy of these results in relation to acceptable criteria; it also should be reviewed and approved by both the RU and SU.

**Common issues**
To avoid common pitfalls in the AMT process, it is important to recognize them:

Unclear method instructions
These are at the root of most common issues. In this case, the RU interprets a method instruction differently than the SU. For example, a method may require the analyst to “prepare a 1-ppm solution,” but PPM can be defined as either gravimetric (µg/g) or volumetric (µg/mL).

Method not written for external use
This issue should be caught during the initial evaluation stage, but many times it is not. An analytical method being transferred should not refer to or rely on any internal documentation or SOPs that are not provided to the RU.

Impurity methods: Relative response factors (RRFs)
When transferring an impurity/degradant method that relies on RRFs, do not assume that RRFs will be the same between laboratories. Always verify the RRFs at the RU.

Arbitrary acceptance criteria
Acceptance criteria must be meaningful and appropriate for the method and should be based on the method’s day-to-day performance. Setting arbitrary criteria can lead to faulty transfers—either in failing a transfer that should have passed from a practical, scientific standpoint based on the method’s historical performance or in passing a transfer that should have failed.

Bias
A commonly overlooked issue is bias in the obtained results. Bias refers to a systematic difference or error of results between the RU and SU. For example, the acceptance criteria for an assay method transfer may require that the RU and the SU data agree within ±1% for triplicate analysis of three lots. The RU data fall within this range, but all results of the RU are 0.8% lower than the SU. While this passes the acceptance criteria, it could still mean that there is a systematic difference or error (bias) associated with the RU data that could result in the RU failing release specifications for the material being tested that should have passed.

**Summary**
Analytical method transfers are a regulatory requirement. A successful AMT requires accurate communication between the transferring and receiving laboratories and a clear plan with defined roles and responsibilities. In most cases, simply asking the right questions can prevent AMT failure. But the most important takeaway is to never treat an AMT as a checkbox routine. Take time to perform a risk analysis that considers the previous experience and knowledge of the RU, the complexity and specifications of the product, and the analytical procedure itself. This small investment will inform decisions about the analytical methods to be transferred, the extent of the transfer activities, and the implementation strategy—and significantly improve the rate of AMT success.