Strategies for Successful Analytical Technology Transfer

Technology transfer (TT) is the formalised process applied when pharmaceutical companies transfer an activity from one location to another. Technology transfer is an expression that most people in the pharmaceutical industry are familiar with or have some experience of. However, ask someone to explain what it is in simple terms and you will probably receive a variety of answers. The need to define a formal TT process arises because of the regulatory, business and ultimately patient risks that an unsuccessful transfer may represent. Additionally, TT is an area of change that regulators will always consider in detail, even if the audit is not a pre-approval inspection.

Therefore, there is a strong requirement to capture and structure documented evidence of the success of the transfer during the TT process and ensure the evidence is secure with no "holes" or "skeletons". For this reason, many companies have implemented formal analytical technology transfer (ATT) processes for analytical testing, as parallel activity to any manufacturing transfer. Some of the common approaches companies have used to support ATT include; formal testing of defined samples at both sites against a protocol and comparison of results by student t-test, applying pharmacopeia analytical methods and collaborative "one team" method development and validation (so it could be argued that both sites are part of the same team, therefore, there are no transfer requirements). There are advantages and disadvantages associated with all of these. Knowledge of common problems that can occur during ATT can mean these are avoided.

Common Analytical Transfer Problems

People who have experience of ATT can probably identify with a range of common problems, which include:

- Poor analytical method robustness
- Different analytical technology
- Different cultures
- Differences in ways of working.

These and many other common problems contribute to differences in analytical results obtained between laboratories. Performing a student t-test in an ATT protocol that statistically demonstrates the non-equivalence of results between laboratories requires careful explanation at the very least, and may document the failure of the transfer. Some differences can be expected, such as subjective tests (e.g. descriptions for appearance and colour measurement), but limited wording in the material specification can still cause problems around this when validation batches are tested. The difference between a compound being described as "*beige*" or "*dark cream*" in a test as simple as an "Appearance" could result in a specification failure! Therefore, specifications need to be worded carefully. Some tests are relative, such as particle size / characterisation, and great care needs to be applied to processes which are particle size sensitive, and the possible comparison of particle size data should be done with caution, even when the same equipment is used by both laboratories. Some data - such as low-level impurities - may not be appropriate for a t-test, and alternative comparison approaches should be used, such as % absolute difference [1].

Differences Between Analytical Laboratories

Fundamentally, fewer "analytical" problems tend to be experienced during ATT when:

- The donor and receiver labs have the same equipment
- The cultures and ways of working are equivalent.

In part, cultural and ways of working differences can be addressed during training. However, these should not be underestimated. Strategically, training has to address two specific needs; provide an appropriate structured framework that generates documented evidence of people being trained (for audit defence reasons) and transfer of tacit knowledge associated with the analytical methodology (so the analysts can successfully use the methods). Additionally, fundamental attitudes towards "following a procedure" or "reporting a problem" can vary with culture and this needs to be considered. How any "Out of Specification" results generated are investigated and reported needs to form part of the TT framework.

The classic problem with differences of equipment (apart from relative tests such as particle size analysis) is HPLC. Something as simple as differences in dwell volume for a gradient HPLC pump can have a profound effect on trace impurities results during gradient HPLC analysis. The primary effect of dwell volume differences is to shift sample retention time[2]. Longer-running HPLC impurities may not be "seen" because a higher dwell volume delays the onset of the gradient and they are not eluted from the column. UHPLC methods (which operate at pressures above 400 bar, 600 psi) are more sensitive to dwell volume effects. Additionally, any analytical method which is not sufficiently robust will cause problems. When gradient HPLC methodology was less common, ATT of a gradient HPLC between Research & Development and a QC laboratory could be troublesome. Basic water quality for gradient HPLC work was a very common early ATT problem. Even when this was recognised, some methods could include peaks present in the blank which were inconsistently variable in size between the sample and blank chromatograms. Trace impurities present in the water can build up on the analytical column when samples are not being analysed, and elute during the gradient. "Proving" that such a peak is an artefact can be very difficult, but can mean the difference between batches passing or failing specification. In this case, if the problem cannot be resolved, then the only way to minimise the impact may be to very carefully control the timing of sample injections, such as running a gradient blank immediately before a sample (so the "artefact" blank peak size is consistent).

Any difference in instrumentation needs to be understood in the context of the analytical method. Additionally, levels of equipment maintenance, standards of instrument qualification and "user

maintenance" all need to be considered. For example, some laboratories change the HPLC lamps after a defined number of hours (using Early Maintenance Feedback counters, EMF, built into the instruments), while others may use the lamp until failure. This could impact the sensitivity achieved, because lamp energy decreases with usage. Therefore, the system suitability criteria for the analytical method should ideally include some assessment of sensitivity or signal to noise. One simple way of achieving this is to include appropriate test samples in the injection sequence used. However, the implementation of Six Sigma and Lean Sigma programmes within the pharmaceutical industry can mean that what might be considered "good chromatography practice" has been cut back to the legal minimum.

The stakes are high for TT because of the potential patient risks that a "poor" transfer would represent, but also because of the potential business impact. Lower cost of manufacturing in locations such as China and India has resulted in significant manufacturing being transferred to these geographic locations. If a manufacturing site produces an API that reaches the end of patent protection, the site must compete with generic manufacturers and will explore a wide variety of means to reduce the cost of goods. It is not uncommon in large pharmaceutical companies for sites to compete internally for new manufacturing processes to be transferred there. A failed transfer under these circumstances could have profound implications for future possible transfers to the site within the network.

Analytical Transfer

The analytical laboratory plays a fundamental role in successful pharmaceutical TT, which is not necessarily always fully understood or perhaps even appreciated. For API manufacturing transfer, there are a large number of analytical testing requirements that need to be satisfied. These can include cleaning validation testing, process development (laboratory samples to support configuration of the process to the manufacturing plant and "user test" samples to support raw materials used), environmental monitoring and any in-process control methodology. These are in addition to any "batches" that need to be tested. All of this can mean that ATT is on the critical path for manufacturing transfer. Therefore, successful ATT can be critical to the success of the overall TT project.

Changes in regulation, such as organisations implementing the 2011 FDA final guidance "Process Validation: General Principles and Practice"[3] are aligned to ICH Q10[4] and include the fundamental principle that:

> "Quality cannot be adequately assured merely by in-process and finished-product inspection or testing."

It has to be designed in to the process. This means a move away from traditional industry interpretation of the 1987 guidance[5] and "three batch validation" for manufacturing processes towards continuous process monitoring[6]. The need to understand the underlying variability of a process will result in fewer TT problems for processes and the greater application of quality by design principles during drug development will tend to push GxP compliance deeper into research and development , where the flexibility to apply appropriate levels of GxP becomes important.

There are many definitions of the role of technology transfer. Here is one from ICH Q10[4, section 3.1.2]:

> "The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement."

The site transferring the technology can be referred to as the donor site, while the site receiving the technology can be referred to as the receiver site. The responsibility for testing any material produced at the receiver site resides with the donor site until the ATT process is signed off. The complexity of the ATT process followed depends on the scale of what is being transferred, but might typically include formalisation of steps such as:

- Information transfer
- Familiarisation
- Training

- Transfer "event" (such as cross-validation)
- Review of the event and decision over the transfer
- Period of active monitoring.

Technology Transfer in the Future

As well as applying the principles of quality by design (QbD) to process design and development, there are a number of applications of QbD principles to analytical methodology[7,8], which should result in more robust methods and fewer TT problems. In Pharmacopeial Forum[9], the United States Pharmacopeia (USP) published a stimulus paper on the application of QbD to the development of analytical methods and proposed new USP general chapters (<220> and <1220>). The evolution of USP methods can be slow because of the need to provide appropriate time for comments, feedback and review/ integrate the information. This can mean regulatory change is perceived as slow. At the same time, laboratories in pharmaceutical companies often report difficulty with keeping up with change[10]. Stimulus papers are typically used by the USP when there is a need to consider a different approach to that currently being applied. A similar "Stimulus Paper Approach" was used by the USP for consideration of changes to the general chapter on Analytical Instrument Qualification (AIQ) <1058>[11]. With a change to a regulatory requirement, such as a change to a USP or Ph.Eur, there is typically a period of uncertainty, part of which relates to not having experience of how regulators will interpret / apply the new regulation during an audit. This uncertainty also applies to ATT.

For laboratory instruments used in GxP environments , the 1987 guidance was diversely interpreted and applied to the qualification on instrumentation in the 4Q model; Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ)[12]. This meant that there are differences in interpretation of what an OQ or PQ might contain, how often they should be performed, and who has responsibility for them. USP <1058>[12] recognises this difference and underneath Table 1 (of <1058>) includes the statement "Performing the activity is far more important than the phase under which the activity is performed". The second edition of the GAMP good practice guide "A Risk-Based Approach to GxP Compliant Laboratory Computerized Systems"[13] and the stimulus paper[11] identify common areas of harmonisation for instrument qualification. However, as QbD-based analytical methods are developed and implemented and transferred, the relationship between the qualification performed on the instrument, the analytical method validation / design space and the QbD-based system suitability criteria will need to be clearly understood.

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