# The Risk Management of Tech Transfer

The medical industry is based on risk management. Do the potential benefits of taking a medication outweigh the potential side effects? Is the benefit of the vaccine worth the risk of the exposure? With every needle prick and every pill swallowed, decisions are made regarding the risk of infection and adverse reactions. Even the touch of a doorknob or push-plate presents a risk assessment. Does my need to pass through this doorway outweigh the probability of transferring an infectious pathogen to my bare skin? In most causes the answer is yes, but this is because of our historical knowledge of the frequency of receiving infections from doors, as well as our experience in assessing the cleanliness of a facility and its personnel. The knowledge and assessment allow us to move ahead in the face of risk. Similar to opening a door, production of a cGMP pharmaceutical, medical device or combination product involves risk assessment and risk management. The technology transfer process is the framework of that risk assessment and risk management.

The interval of technology transfer process can be defined as starting with the initial client/CMO meeting and ending with issuance of the cGMP record for execution. All of the activities that occur between those two points are meant to minimize risk during the production of the product and ultimately to the end user. Risk in producing a cGMP product is shared by the client and the CMO, but will primarily fall on the CMO as the owner and executor of the technology transfer. Production of cGMP products is typically viewed as a rigid process, adhering to regulatory guidelines and abhorring deviations. Ironically, for a CMO to be viewed as a minimizer of risk in the production of cGMP products, it must be flexible in its ability to handle technology transfer.

Technology Transfer: The Flexible Framework of Firm Success

With the large variety of pharmaceutical/biotech products in early stages of clinical and process development, the most valuable skill a contact manufacturer can have is flexibility. Pharmaceuticals, medical devices and combination products seeking a competitive edge in niche markets require an ever-growing level of customization in contract services. Beyond the differences in the products themselves, available background information, expertise and experience with the products may vary significantly. Ranging from early-stage virtual companies and new acquisitions of large pharma firms to companies with long development histories, available equipment and thorough documentation, the technology transfer process is driven by the availability of knowledge, information and hardware.

The standard goal of every client is the production of in-specification cGMP material at minimal cost in minimum time. The cost and timing is contingent on the amount of information and hardware — and therefore risk — that needs to be transferred. Whether the material is in-specification depends on the quality of the transfer. A very basic technology transfer model is the filling of a sterile pre-formulated bulk drug product. The required flexibility is minimal, as is risk. The work necessary before issuance of an executable cGMP record is nil, given that the CMO has established batch record templates, validated media fills in place, and fill components available. As the complexity of the process/product increases, so must the risk assessment and flexibility of the CMO.

Every process should have certain areas examined or addressed at a minimum for a successful technology transfer. These areas make up the flexible framework for the technology transfer. The areas below are listed essentially in chronological order, but activities can be intertwined or run in parallel.

At the initial meeting, most aspects regarding the need, timing and scope of the following should be discussed or finalized:

EH&S evaluation

Given that the CMO is a multiple product facility, each new product should be evaluated with respect to Environmental Health and Safety. Information such as personal protective equipment, handling instructions, and solubilizing and deactivating agents should be determined and presented in a form that can be made available to all departments and personnel who may come into contact with the product. Depending on the product, studies may have to be performed to validate the deactivating agents and procedures. This can present additional cost and timing to a technology transfer. In addition, the studies should be considered when planning execution of later activities, due to the need for the evaluation information during any API/product handling. The EH&S evaluation is the first line of risk management in the technology transfer, with the intent of protecting those who will be producing the product.

Incoming Material Specifications

What may seem like one of the more basic elements of a technology transfer can often provide the most complexity and unforeseen delays. Incoming material specifications act as the first line of risk management for the product by ensuring that what is delivered for manufacture of the product meets the requirements for what is needed for manufacture of the product. This starts with an agreement on what is required. There are many standards for material testing: USP, EP, JP, Multicompen-dial, ASTM, etc. The testing required in the material specifications should meet the requirements for the relevant regulatory bodies, but not be excessive, as this will drive up cost and potentially cause delays while waiting for superfluous testing results. The decisions in this subtask of material specification is a risk management exercise in itself. The exercise is more difficult for new APIs or drug substance, which are still outside of the pharmacopoeia guidelines.

With any unique APIs or excipients comes additional tasks that have to be managed within the material specification. This includes supplier audits, analytical method transfer(s), third party laboratory audits, sample management/tracking, lot sampling/satellite samples, and more. Each of these tasks presents its own risk management and is a source of cost and delay. While many of these activities can be executed in parallel, the availability of full released materials is often the final bottleneck to be cleared. The best option is accepting the materials previously approved by the CMO. The flexible CMO will have available an extensive library of pharmaceutical grade chemicals and components available from approved suppliers. The knowledgeable client will know whether these chemicals and components will be acceptable for the product/process. In summary, this aspect of the technology transfer — which runs the entirety of the technology transfer process — relies heavily on the knowledge, experience, and flexibility of those involved, with higher amounts of each increasing the rate of success and lowering risk to the final product.

Analytical Method Transfers

Transfer of analytical methods is an aspect of technology transfer that strongly affects downstream activities. Aside from the aforementioned transfer of material specification testing, the transfer of in-process testing methods can affect feasibility, engineering runs, and the planning of the cGMP batch. This in turn affects the ability to design and validate equipment, and develop processing techniques, and documentation. Care must be taken in the early stages of the technology transfer to communicate the status/state of all analytical methods to be transferred, reagents and equipment necessary for testing, and the need for either verification, qualification or validation of the method.

Development Work (Feasibility, etc.)

The basis of CMO development work is almost solely the reduction of risk. The more experience with a product/process that can be gained by the CMO, the lower the risk. Most clients have a process or an idea of a process for their product, but even if the unknowns are ‘knowns’ to the client, everything reverts to an unknown when transferring a process to a CMO. Will the process work in the CMO’s facility? Will the equipment produce the same results?

This is also the stage of technology transfer that could be termed Process Conceptualization (or perhaps more accurately Process Re-conceptualization). This is the first step in integrating the client process into the CMO facility. In most cases, what was previously a bench-top process must now be redesigned for aseptic processing in a sterile environment. Major process design issues may be considered, such as type, size, and materials for vessels and piping/tubing, unit operation equipment selection (i.e. mixing, filtration, microfluidization), the use of disposable equipment and components, materials of construction of product contact surfaces, order of operations that facilitate sterile production, modes of fluid transfer, and initial process parameters and process conditions. With this initial conceptualization, consideration should be given to the necessary validation work that will follow if the decision is made to continue with a particular order of operations or configuration.

Execution of development work with the conceptualized pro-cess may occur at a later time. The actual execution may depend on other factors, such as availability of raw materials, equipment procurement, IQ/OQ of equipment, and transfer of analytical methods for in-process testing. The actual execution marks the first attempt at formulating and/or filling a product. This is ideally when issues should be discovered and resolved. During execution, additional design issues may also be considered, such as material flow, process timing, and sampling techniques.

The objective of the development work is to minimize risk during execution of the clinical batch. Obviously, if the process is very simple or well established, much of this work can be avoided.

Equipment Selection/Procurement

The selection/procurement of equipment is more of a factor in the cost and timing of the technology transfer process than reduction of risk, but can be significant to both. The primary concern in equipment procurement is cost and lead time. If the option for disposable equipment and components is available, it is the advisable choice. The cost and lead time for an average early phase clinical scale stainless steel vessel is $8,000 and eight weeks. An equivalent glass vessel or polymer container would be less than $2,000 and two or three weeks, if not already in stock. Glass is a particularly good option because of its inert surface characteristics and the ability to make custom modifications very quickly. While the advantage of the cost and time differential is obvious, the selection of disposables also allows for the elimination of cleaning validation and IQ/OQ of reusable equipment. The risk reduction of the disposables comes from the elimination of potential contamination issues that arise from cleaning reusable equipment and from production in a multi-product facility. The options in equipment selection/procurement rely heavily on the degrees of freedom developed in process conceptualization. The impact of equipment selection/procurement should not be overlooked when performing process conceptualization.

Validation

The most significant (and mandatory) element of risk reduction is validation. Validation is the evidence that when instructions are followed, no one gets hurt. Validation is a much larger concept than will be covered here. We will only touch on the highlights that are relevant to risk reduction as it relates to technology transfer. Not all of the types of validation may be necessary for every process/product, but that in itself is a risk management decision.The real challenge of validation is to design the validation protocols such that limited sets of data (typically n=3) provide conclusions so robust that the results can be then be anticipated without further confirmation testing, i.e. the results will happen every time including during a clinical cGMP batch/lot.

The design of the validation protocol is contingent on the knowledge of the final process. All validations must closely mimic, if not exactly replicate, process conditions, including equipment to be used, material and personnel flows, equipment set-up, and validation-relevant parameters such as hold times and filtration conditions.

**Cleaning:** Cleaning validation is only relevant if the process necessitates reusable equipment such as stainless steel vessels, pump elements, piping, etc. This effort should precede any use of the active agents in question. The cleaning validation conditions must take into consideration the realistic applicability in the specific manufacturing environment, i.e. availability of deactivating/solubilizing/cleaning agents, total volumes to be used during actual cleaning, and capture and disposal of waste. Additionally, chemicals other than solvents should not be used on product contact surfaces, as residual bleach and other harsh chemicals may have deleterious effects.

**IOQ:** The IOQ is a typically a basic validation exercise involving verification that the equipment delivered for the processing/manufacture of a product meets the specifications and operational requirements previously determined as necessary. Most significant issues can be anticipated during the generation of the validation protocol. Knowledge or investigation of items such as utility requirements as compared to facility limitations prior to protocol design is valuable in preventing unnecessary delays. The IOQ should be executed and resolved before the initiation of any development or feasibility work.

**SQ:** Sterilization qualification (SQ) refers to validation of sterilization techniques such as autoclaving, depyrogeneration, or steam-in-place (SIP). This typically involves components unique to the client that could not otherwise be “bracketed” or included in any previous CMO sterilization validations. With respect to the flow of technology transfer, the SQ(s) can be executed at various times, if given maximum equipment requirements are known. For example, when validating an autoclave load and cycle, the validation can still be used if items are removed from the load, but if items are added, the validation must be repeated. Planning validations with this principle in mind can save time upfront and prevent the need for repeating a time-consuming validation. At a minimum, SQ(s) must be completed before the aseptic processing validation and the cGMP batch.

**APV:** Aseptic process validation (APV) refers to growth media runs (n=3) meant to validate the aseptic nature of processing steps that do not fall under validation work previously performed by the CMO. Typically, this involves client-specific transfers and manipulations performed while the product or components need to have sterility maintained. During Process Conception, the need for an APV of any aseptic transfers or manipulations should be evaluated. The execution of aseptic process validations should occur after the Engineering Run and be as representative of the final clinical process as possible. Ideally, the final cGMP batch record would be reformatted as a protocol using growth media in place of product specific raw materials. Incubation times for each run of growth media should be considered and built into the overall tech transfer timeline.

**PQ, PV:** Process Qualification (PQ) is a validation that the process can yield product at the necessary specifications. This primarily relates to small scale, early phase clinical work and can often be done in conjunction with the Engineering Run. PQ is often included in discussions of IOQ, but may occur at a later time depending on process complexity and API availability. Process Validation (PV) is a larger scope validation typically relating to commercial scale manufacturing. This validation is meant to demonstrate the necessary robustness of the process to produce in-specification product at various processing extremes. The validation will draw upon all historical knowledge of previous runs and development work performed both inside and outside of the CMO. Developing a robust PV can be a large endeavor, so this may be a primary focus of technical transfer for a commercial scale product.

Engineering Run

The final opportunity to reduce risk is the Engineering Run, which is an execution of the cGMP batch record under non-cGMP conditions. This allows for any final updates to documentation or processing steps before the cGMP execution. Confidence in the successful execution of the cGMP batch record should be very high coming out of the Engineering Run. It is best to execute the cGMP fairly quickly after the Engineering Run to allow the familiarity of the training exercise to stay fresh.

cGMP Issuance

At this point the technology transfer is complete and the cGMP batch record is ready for issuance and execution.

Conclusion: Acceptable Risk

Nothing is without risk, but a successful technology transfer process will minimize risk to an acceptable level. Each product will have its own unique reasons for risk management, which can be dealt with by combinations of the aforementioned areas of focus. Those combinations will require flexibility that is directly proportional to the risk. Through experience and the ability to handle non-standard situations, the flexible CMO will be able to successfully negotiate technology transfer.