

Integrating Technology Transfer and Facilities Startup for Biologics

Careful planning, adequate staffing levels, and experienced project managers can help avoid pitfalls of transferring processes from one facility to another.

Compared with the 10 or so years required to develop a drug and the many years a successful biologic will remain in commercial production, technology transfer and facility start-up may seem like a mere blip in the lifecycle. But the seamless and integrated execution of technology transfer and facility startup can make all the difference between a successful product launch and one plagued by delays, rework, costly overruns, and millions of dollars in foregone sales.

Poorly handled technology transfer can have a long-term impact on process capability, process performance, and compliance. Shortcuts on the compliance side can affect the outcome of regulatory pre-approval inspections (PAI) required when changing to a new manufacturing site, and can significantly delay product approval timelines, which again can impact revenue and profit. In the worst case, the organization may be unable to obtain licensure for the facility.

Consider the economics for a biologic with expected annual sales of \$1 billion. Every month lost during technology transfer/facility start-up carries a price tag of \$80 million. No matter the reason for delay—technical problems, inadequate project management, or compliance issues—the result is the same: significant destruction of value.

Getting transfer and start-up right is a daunting challenge. A high and reliable level of supervision, diligence, perseverance, and communication with all participants and stakeholders must be achieved throughout the transfer of the product as well as inception, design, build, commissioning, equipment qualification, and process validation phases, through submission and PAI. There are thou-

sands of details that must be planned for and checked and an equal number of opportunities for disaster. The most serious problems occur for three reasons: the failure to integrate quality and compliance with technology transfer from the onset, lack of understanding of tasks or requirements, and inadequate project management.

Many organizations complete the transfer first and only then address quality and compliance, despite the demonstrated pitfalls of the approach. Further, many organizations lack a sufficient number of qualified and experienced internal project managers and often underestimate the complexity of these projects. Biologic transfer and facility start-up are complex, interdisciplinary endeavors that require sound planning and project management guided by an in-depth understanding of technical and regulatory requirements and, crucially, the tight integration and coordination of the many processes involved.

TECHNOLOGY TRANSFER COMPLEXITIES

Technology transfer typically includes a change in location, ranging from a move between different facilities on the same campus or between locations on different continents; it often includes a manufacturing scale-up. In an environment with specialized contract manufacturing organizations (CMOs) and contract testing laboratories (CTLs) and the need to control capital investment and minimize time to market, the start-up of commercial manufacturing often requires more than a single technology transfer between two sites. More likely, multiple transfers need to be coordinated to meet start-up timelines, launch dates, and manufacturing capacity expectations.

Technology transfers typically include the following elements:



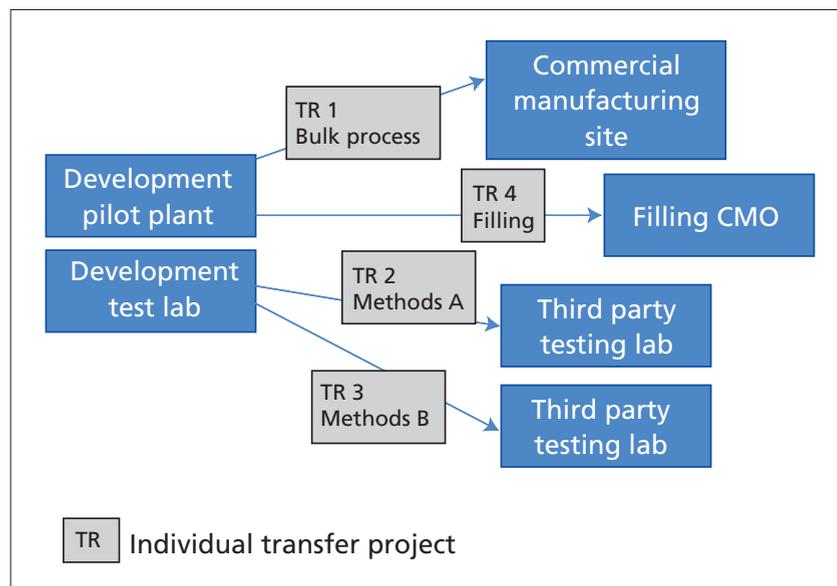
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- Transfer of the bulk manufacturing process from the development pilot plant to the commercial manufacturing site
- Transfer of filling operations from the development pilot plant to a CMO
- Transfer of analytical methods from the development test laboratory to the commercial manufacturing site laboratory or to a CTL.

As shown in **Figure 1**, technology transfer can easily entail four or more different transfer projects, creating a highly tangled web of pre-requisites and inter-dependencies that have to be aligned, coordinated, and managed simultaneously to ensure a successful transfer.

Unlike the transfer from one commercial manufacturing site to another for products already in-market, technology transfer for development products requires transition from a development environment into a GMP environment. From a product lifecycle perspective, this stage might be seen as the new product's adolescence. And as one knows, nearly everything changes during adolescence. To get through these growing pains, the technology transfer should demonstrate that the receiving site is capable of manufacturing the product within predefined acceptance criteria. It should follow a planned and documented approach that defines specific requirements of the sending site and the receiving site. The process at the sending site should be qualified, which requires a "frozen" process description and the definition of critical quality attributes (CQA) and of critical process parameters (CPP). The plan should also include a list of process equipment used at the sending site and equipment sizing information and a complete list of materials and

Figure 1: Technology transfer example.



suppliers. If the transfer includes a change in process scale, scale-up parameters should be defined as well, based on a sound process understanding gained during the development stage. Scale-up parameters may include:

- Volume-to-surface ratio of process tanks for mixing steps with or without heat transfer
- Volume-to-membrane-surface ratio for ultra- and microfiltration steps
- Cooling rates for freezing processes
- Constant bed heights and process cycles for chromatographic steps.

These are just a few of the aspects of process understanding from the development stage that must be transferred into a robust and reproducible GMP process for commercial manufacturing. It requires excellent coordination between development scientists, process engineers, and design engineers and a structured approach specified in sufficient detail in a well-defined technology transfer plan (TTP).

The TTP should do the following:

- Define the process parameters and key equipment specifications for the receiving site
- Lay out the transfer steps and the training requirements for personnel from the receiving site, which whenever feasible should include on-site training at the sending site
- Specify the expectations and target acceptance criteria for the engineering runs at the receiving site.

It is of utmost importance that this process be managed through a sound change-control process with supporting documentation control. Manufacturing standard operating procedures (SOPs) should be available in draft form as well as the master batch records, which will be "red-lined" during the engineering run to reflect all essential process details specific to equipment and the process at the receiving site.

The transfer of the analytical methods from the development test laboratory to the testing laboratory at the receiving site and/or

to a CTL should be defined in an analytical method transfer plan. One should also assure that adequate testing capabilities are in place in time to support the technology transfer.

GMP OPERATION AND PROCESS PERFORMANCE QUALIFICATION

Once engineering runs at the receiving site have been successfully performed, the receiving site should be brought into a state where it can operate under GMPs. This means that qualified staff (including management oversight) are available, process equipment and utilities have been qualified and, ideally, the performance qualification (PQ) of critical utilities has been completed. At a minimum, the utility PQ runs should have produced at least acceptable initial results. Operating under GMPs also means that quality systems have been implemented, including:

- Change control
- Document management
- Deviation/investigation management
- Product disposition.

All qualification and validation activities at the receiving site should be governed by a validation master plan (VMP). Quality agreements should be in place with CMOs and CTLs involved in a technology transfer program, with adequate oversight and supported by a vendor management program that includes quality audits.

The final step of the technology transfer comes with the process performance qualification runs (PPQ) at the receiving site. These runs establish the ability of the receiving site to manufacture the transferred product in accordance with GMPs. Extended in-process testing provides the objective evidence to demonstrate that CQAs and CPPs are being met and estab-

lish the basis for in-process ranges for routine process monitoring and continued process verification (CPV).

THE INTEGRATOR: PROJECT MANAGEMENT

Ultimately, the key to integrating technology transfer and facility start-up lies in strong project management. Strong project management includes the implementation of project management tools that monitor and control activities, establish appropriate milestones and deliverables for each step of the way, and ensure an on-time and on-budget transfer and start-up. At the same time, careful project management ensures regulatory compliance with national and international requirements as well as applicable ICH guidelines, integrating project oversight and quality management.

Doing the job correctly requires a significant commitment in planning, resources, and know-how. A critical core of knowledgeable and experienced personnel is needed to support the implementation of the work at all levels, from planning and process development to the hands-on execution of tasks. Some people must have technical competencies to support utilities and equipment qualification, process validation, and related tasks. Others need to be highly skilled and experienced project managers who have successfully navigated such projects previously.

Many organizations have limited internal resources and lack people with the requisite expertise and experience. And many senior executives believe that virtually any good project manager can oversee projects of this type. Every technology transfer and facility start-up project, however, has its own set of challenges, some of which are less familiar to the

average project manager than others. That's when experience counts. It can often mean the difference between significant and costly delays and cost overruns versus the successful and on-time transfer and start-up. In addition to knowledge and experience, project managers must have the time and availability to devote to the project, and have adequate staffing to cover the activities that must be planned, overseen, and implemented.

Having a sound and comprehensive project management in place, an understanding of the complex activities that must be coordinated, and a determination to integrate the entire transfer and start-up process, will not only shorten time to market and avoid costly mistakes but also gain a repeatable, best-practices transfer capability for the future. ♦