Considerations for successful tech transfer of a biologics upstream process

Bioprocess experts from Lonza discuss how molecular format and the product lifecycle phase impact the process, risks and outcomes of upstream technology transfer of biologics.

The emergence of huge pharmaceutial companies with discrete centres of excellence in geographically dispersed locations has upended the classic model of one-stop shopping for all development functions.

The inevitable shift to external manufacturing sites necessitates a seamless technology transfer process, and should incorporate unique perspectives on local approaches to knowledge transfer, quality, regulatory and all other operational requirements pertaining to the site's locality. Success requires close attention to the principles of tech transfer to ensure the smoothest path to market.

A clear and comprehensive definition of technology transfer is outlined in ICH Q10:

"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 realization. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach, and ongoing continual improvement".

It also requires active management of the transfer process, which spans small-scale process development, an intermediary pilot scale and subsequent transfer to either a clinical or commercial manufacturing plant internally or externally.

An example upstream cell-culture process to generate drug substance is depicted in **Figure 1**.

Growing need for technology transfer

A structured and modular approach provides flexibility, consistency and agility, serving the ever evolving market needs to ensure success.

An example of the structured and modular tech transfer approach is shown in **Figure 2**.

Technology transfer roadmap

A pharmaceutical company could engage a contract development manufacturing organisation (CDMO) for tech transfer at different stages of the product lifecycle. Several possible ingress points are illustrated in **Figure 3**.

Key to the success of a product is a concurrent transfer of technology, process information and skills gathered at every step of discovery, development and commercialisation. Tech transfer plays an important role in documenting all of the active and tacit knowledge gathered at each step and provides an effective way to hand over the information to the receiving partner.

Five major activities carried out by a tech transfer team for a thorough transfer of any project type (clinical or commercial) and to single-use or stainless-steel facilities is illustrated in **Figure 4**.

Common upstream challenges and solutions

The key barriers to a successful tech transfer process are technical (complexity, equivocality and concreteness) and human (communication, motivation and distance).

One of the most critical aspects is the ability to operate fluidly between bioreactor scales, a task made more challenging when scaling up to large-scale manufacture of biotherapeutics. This is underpinned by aligning tightly with established process parameters that are scale-independent (ie, pH, dissolved oxygen (DO)), in addition to a methodical evaluation of product quality characteristics and product quality attributes.

In the absence of basic process understanding, expertise and knowledge of key and critical process parameters, as well as related tech transfer elements, processes can be significantly delayed and in some instances, fail to launch. With upstream processing, it is critical to select, develop and occassionally optimise media and cell culture »

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His career has spanned various roles including brand protection utilising novel technologies at De La Rue, to numerous QC, scientist and project management roles in Eli Lilly, Patheon (now Thermo Fisher), Catalent and Porton Biopharma.

Neil obtained a degree in medicinal and pharmaceutical chemistry from Loughborough University.

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Maolong Liu is Head of Manufacturing Science and Technology (MSAT) at Lonza Biologics' Singapore Site, ensuring excellence in mammalian manufacturing processes.

Over the last 13 years, he has developed an in-depth expertise in facility startup, tech transfer in 1kL, 2kL and 20kL as well as process development and improvements. Maolong holds a master's degree in chemical engineering from Massachusetts Institute of Technology.

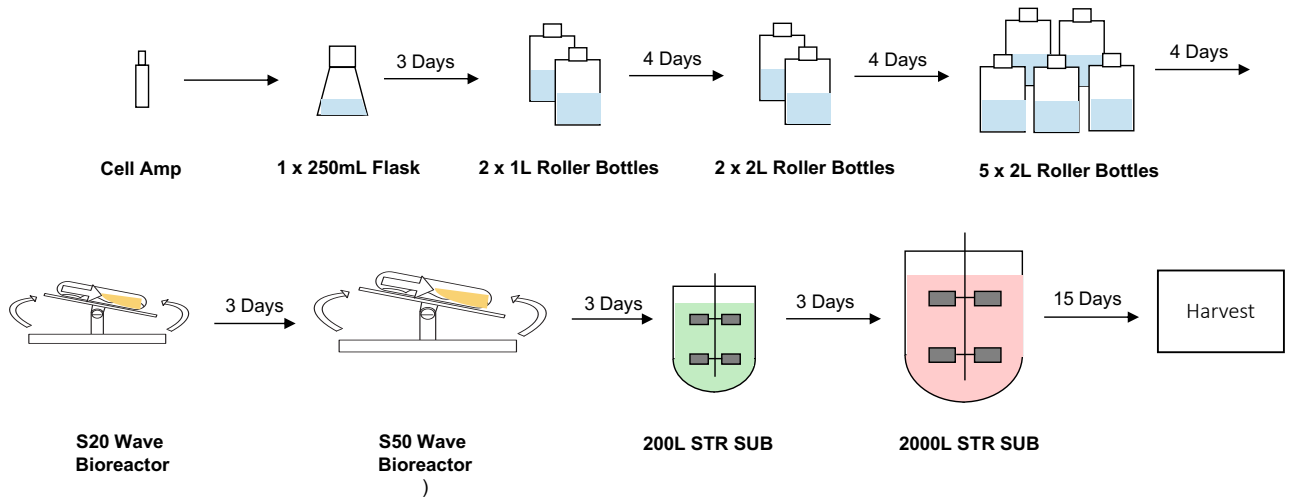

Figure 1: Example upstream cell-culture process to generate drug substance.

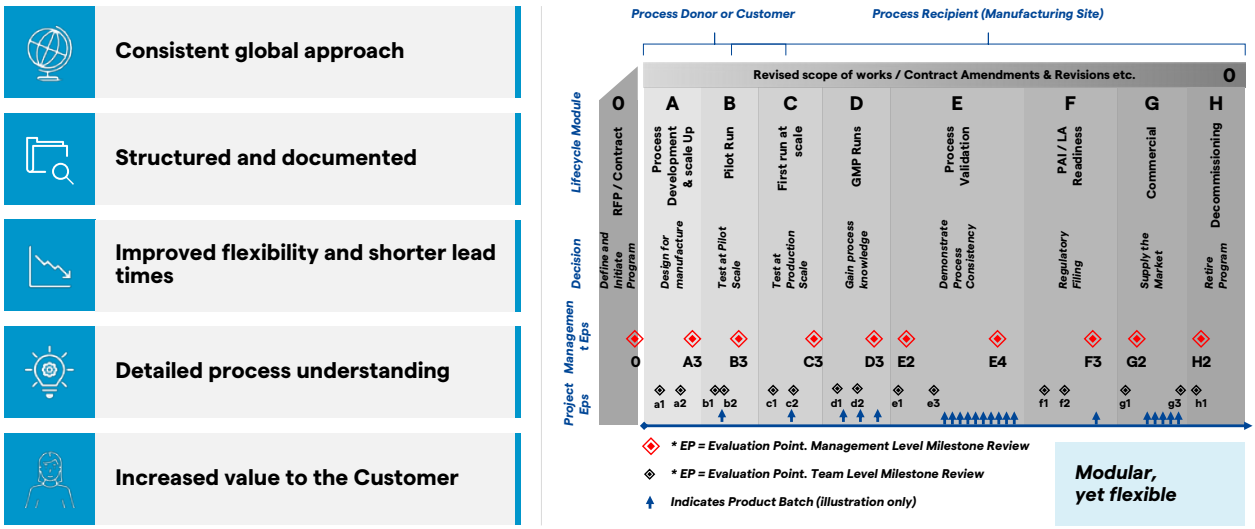

Figure 2: Example of a structured and modular technology transfer approach based on market needs.

operations leveraging quality by design (QbD) concepts and design of experiment (DoE) studies. It is also critical to evaluate scale-dependent parameters and optimise for scalability and process robustness.

A common challenge encountered in bioreactor scale-up arises when the geometry changes between the sites or from small-scale process development to at-scale production. In addition, differences in mixing and aeration strategies between vessels can impact cell culture kinetics.

Efficient mass transfer is critical for cell metabolism, and this is determined through volumetric mass transfer coefficient (kLA) experiments on the bioreactor to understand equipment capability. Initial tech transfer steps include aligning the customer's power per unit volume (P/V) specification and gas sparge strategy.

Prior to running a process at scale, the specific sparge strategy is first verified at small scale and then executed at the larger scale. In addition, engineering runs are often performed at scale before progressing to drug substance manufacture for either clinical or commercial supply. It is also important to consider the scale differences in gassing efficiencies to control the pH and pCO_2 level, which may be sensitive to cell growth, process performance and/or productivity. Having development, process equipment and automation knowledge, as well as a robust at-scale strategy to control the process attributes, drives success in scaling up for upstream tech transfer.

Another important aspect to consider is having a detailed gap analysis, a practice that contrasts likely or anticipated performance with empirical results, the output of which not only identifies risk but, more importantly, proactively mitigates

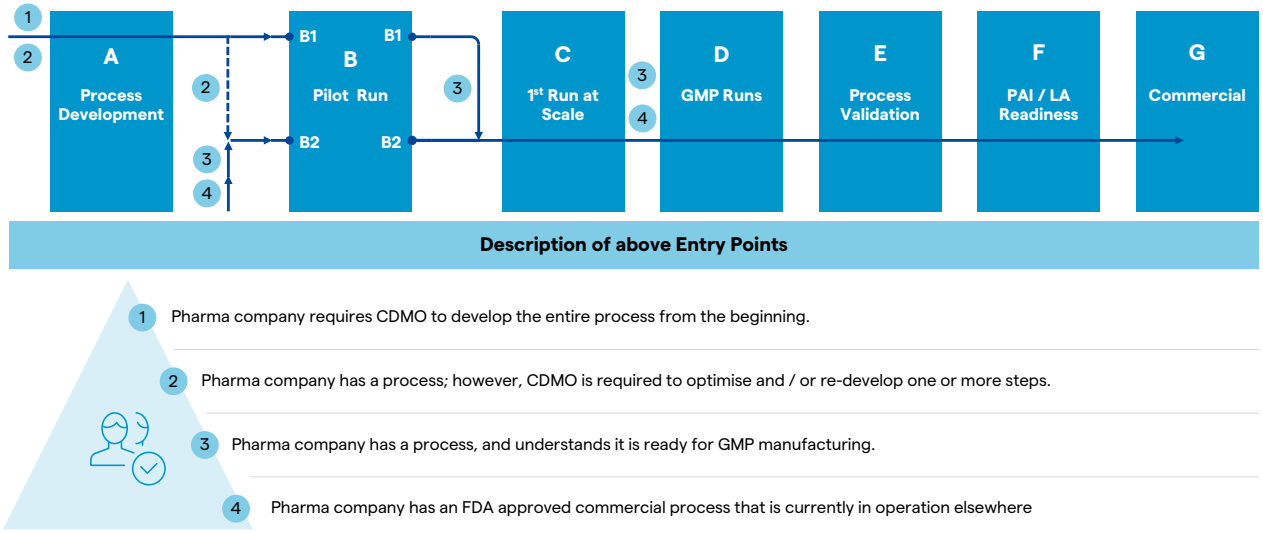

Figure 3: Entry points of technology transfer at various stages of the product lifecycle.

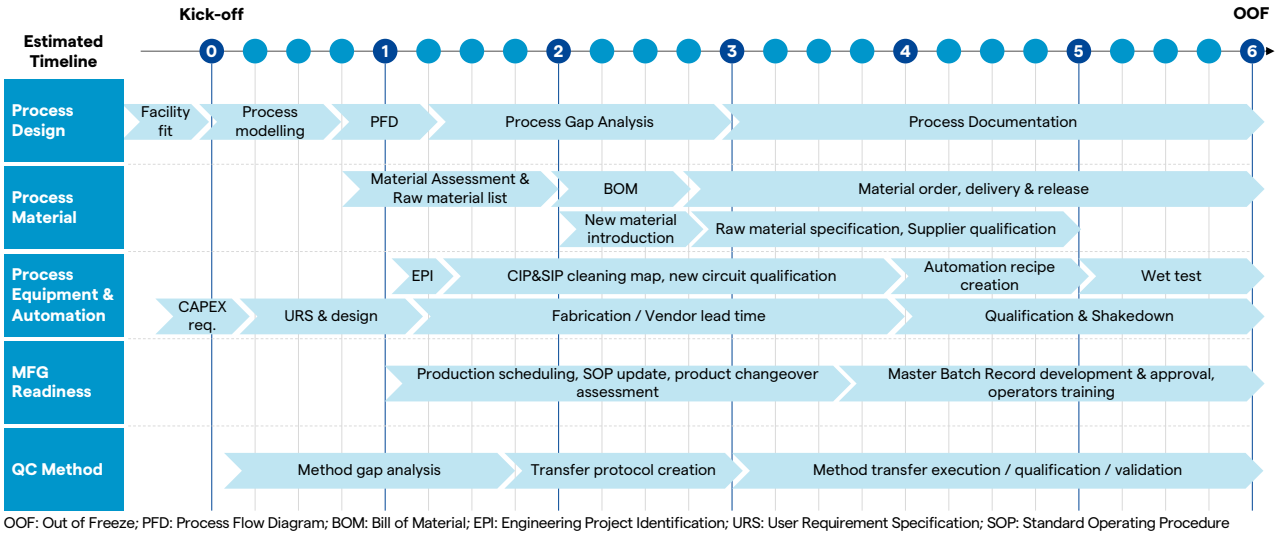

Figure 4: Example of major activities carried out by a tech transfer project team for a thorough transfer (Mfg = Manufacturing, QC = Quality Control, CAPEX = Capital Expenditures, CIP = Clean in Place, SIP = Steam in Place).

it to enable a successful outcome. This exercise represents a thorough approach to understand the development history by the process donor, and the differences between donor and receiver in the use of process instruments and equipment, as well as in operational details.

Examples to consider are pH and DO probes, metabolite analysers, cell counting methods and instruments, differences in cell bags, single-use versus stainless-steel bioreactor designs and contact materials. Maintaining the same instrument and equipment types is often not possible for cross-company transfers. The gap analysis should also encompass comprehensive risk identification, risk assessment and risk mitigation for gaps. Action plans with expected outcome and due dates are to be established as part of technology transfer, which may often require equipment wet testing and small-scale laboratory studies.

There are increasing challenges and pressures to tech transfer, as the need for speed to market is balanced with the introduction of process improvements for higher throughput (titer and yield) and lower cost of goods (cheaper media, resins, etc), thus delaying 'process lock' as late as possible. Accelerated timelines are possible with parallel process development and tech transfer, leveraging a CDMO's platform process knowledge, network capabilities and expertise.

An example is illustrated in **Figure 5**, where concurrent cell line development, process development and tech transfer were completed within a seven-month time frame, delivering an improved titer performance up to 75 percent.

The last important factor to consider is well characterised and developed scale-down models for large-scale bioreactors. This case study from Lonza, illustrated in »

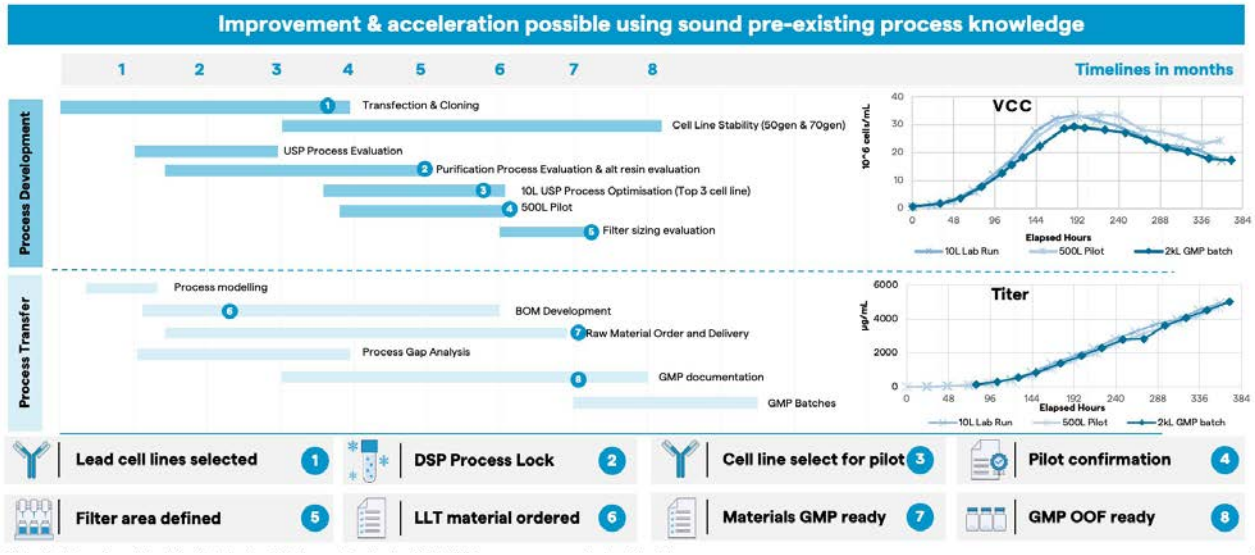

Figure 5: A Lonza case study for parallel cell line development, process development and tech transfer.

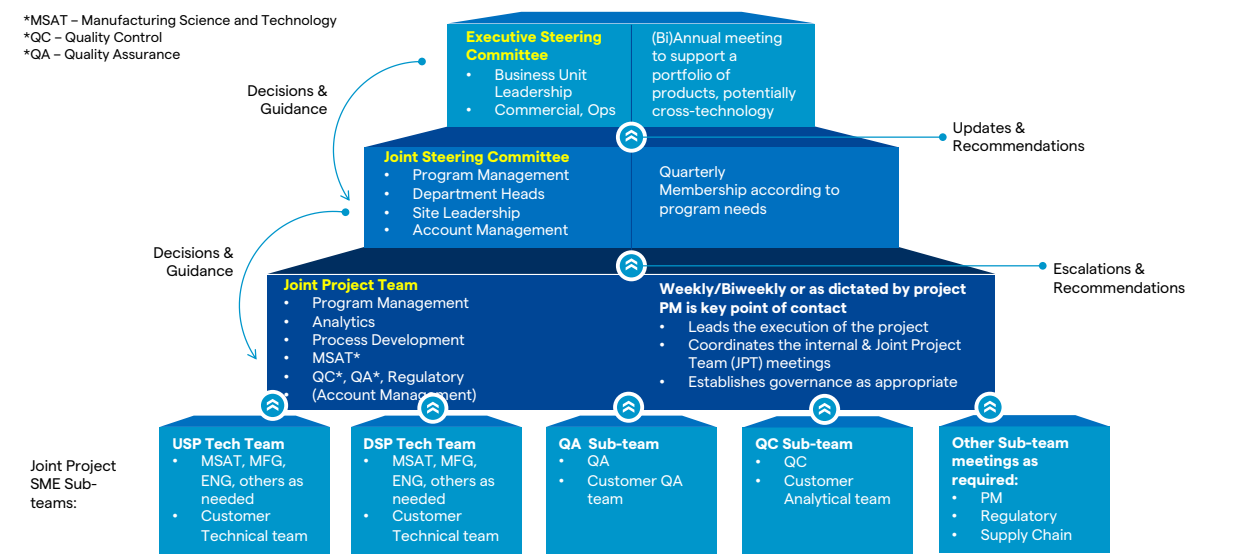

Figure 6: Example of governance structure for tech transfer into CDMOs.

Figure 5, demonstrated consistency from the lab, at pilot and up to GMP scale in cell growth, process performance (including titer) and product quality.

Communication and collaboration

Lastly, a well-defined communication plan must be established as early as possible in the programme with defined and specific roles for every member. By starting collaborations early, relationships are initiated and involvement in the project happens during inception, leading to ownership and thereby maximising results. Having a person in plant for some tech transfers facilitates higher levels of communication.

Furthermore, leveraging good project management skills such as proper documentation is central to capturing important elements of the transfer and paving the path to producing reproducible processes irrespective of their complexity.

A clear and effective governance structure is the key enabler of success. An example of governane structure for tech transfer into CDMOs is illustrated in **Figure 6**.

Overall, the ability to maintain an end-to-end view of the tech transfer process, and use this understanding to effectively balance competing priorities, allows teams to drive for the best overall value realisation to advance biopharmaceutical therapies.

Nikki Nogal

Nikki Nogal is Global Director of Technical and CMC at Lonza.

She brings more than 20 years of experience in pre-discovery through the lifecycle management of mature products at various companies including Gilead, Genentech and Abzena.

Nikki earned both BS and MS degrees in chemical engineering at the University of Maryland and a PhD in biomedical engineering from Florida State University. She completed post-doctoral training at Johnson & Johnson and the University of California San Diego in pharmacology and bioengineering. She holds an adjunct faculty appointment at the University of California San Diego.