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# Managing Technology Transfer for Cost-Effective Development and Manufacturing of Biopharmaceuticals

By ALLAN WATKINSON

In today's aggressive biopharmaceutical market, many drug discovery organizations, including both big pharmaceutical companies and small technology start-up companies, are outsourcing the development and manufacturing of their biopharmaceuticals to specialized contract manufacturing organizations (CMOs). Outsourced biopharmaceuticals range from those in early phase production to products that are well advanced down the development pipeline. As a result, there has been an expansion of CMOs that specialize in all aspects of biopharmaceutical manufacture, from process invention and development, through small-scale GMP production, to process validation and large-scale manufacture. The CMOs provide R&D services, quality function, and state-of-the-art good manufacturing practice (GMP) facilities needed for the production of biopharmaceuticals (Figures 1 and 2). Using CMOs for biopharmaceutical process development and manufacture provides major cost savings by dispensing with the need to invest in experienced personnel and expensive manufacturing facilities.

Whether the project is a limited piece of development work or involves extensive resources leading to biopharmaceutical manufacture, information must be transferred from the parent organization to the CMO in order to perform such services. This is known

as technology transfer, often abbreviated as "tech transfer." This article describes the technology transfer process and provides a framework for maximising the transfer efficiency and reducing costs.

## Technology Transfer: A Definition

There are a variety of ways to define technology transfer. However, the definition we feel is most appropriate is as follows: Technology transfer is a "wide set of 'processes' that manage the flow of knowledge, experience, know-how, reagents, and equipment between the sending organization and the receiving organization, leading to an actual demonstration of transfer."

This definition recognizes that technology transfer is typically not a single process, but a complex of interlinked exercises that transfer a process from the sending organization to the receiving organization. This is usually, but not always, from drug discoverer to CMO but can also involve technology transfer within an organisation (i.e., between R&D and manufacturing). This definition also recognizes that technology transfer can encompass a wide range of transfer activities. At its simplest, tech transfer can be perceived as sending a simple set of instructions. For example, technology transfer can be as minimal as the transference of the instructions for a basic assay. However, it is broader than that: it is about the swapping of technological experience that is essential to make the set of instructions function with maximum efficiency. Certainly, written descriptions rarely convey all that is known about a



Figure 1. CMO Manufacturing Capability: Avecia's ABC5000 GMP Microbial Facility.



Figure 2. GMP Media Make-up Suite with GMP Manufacturing Facility.

**Allan Watkinson, Ph.D.** ([allan.watkinson@avecia.com](mailto:allan.watkinson@avecia.com)), is a senior research scientist and principal investigator at Avecia Biotechnology, Billingham, UK. This article is based on a presentation given at the Williamsburg BioProcessing Foundation's Raw Materials and Contract Services for Mammalian Cell Products meeting held in Buffalo, NY, July 12–14, 2004.



process used to successfully manufacture a product. Such instructions omit the underlying assumptions and the element of human experience or understanding that is essential for a process to function as planned.

In addition to 'know how,' the technology transfer process can involve the transfer of more tangible items such as specific reagents, cell banks, or even crucial pieces of instrumentation. Technology transfer may also involve the transfer of a specific gene sequence or an engineered recombinant host organism. For some specific assays, essential reagents (e.g., antibodies) may be required.

Finally, this definition of technology transfer recognizes that it is simply not just about transferring information. Successful transfer must be demonstrated: technology transfer is more than a paper exercise — it must yield physical results.

### Technology Transfer: Principles

It cannot be overstated that the overarching principle for technology transfer is good communication. Effective communication is required on several levels: 1) between organizations; 2) between functional teams within each of the participating organizations; and 3) between individuals. Consequently,

technology transfer activities permeate throughout several strata of each organization.

It may be self-evident that technology transfer is all about communication, but it would be wrong to suppose that it simply represents a one-way flow, with the contractor sending instructions regarding how to run a process or assay to the CMO. In reality, technology transfer represents a partnership between stakeholders that involves a complex interactive process with a great deal of back and forth exchange. As such, during technology transfer there is a flow of instructions/information between two or more units, irrespective of their size.

One reason for this bidirectional information flow is that to understand and operate the processes being transferred usually requires significant learning on the part of the CMO. This is an iterative process with inputs from both parties. Another reason is that adaptation may be required, because direct transfer into the CMO facility may not be an option (*i.e.*, equipment may be different or the capacity of the plant may be limited at a particular step in the process). Adapting a process is also an iterative matter and requires two-way communication for successful technology transfer.

When the contractor and the CMO are separated by structural, cultural, time zones and organizational boundaries within their respective organizations, significant complications arise that often hinder successful technology transfer. Each organization has its own functional structures and political/business systems, and if potential issues are not recognized and addressed, such boundaries can inhibit the flow of information. Therefore, measures must be put in place to ensure that these issues do not interfere. Similarly, technology transfer should not reside solely with senior management, but must be allowed to permeate throughout several strata of each organization in order to ensure that the relevant personnel are involved. Such a structure does have a downside: it can become difficult to control the flow of information, and vital pieces of information may not be shared at all levels, potentially bypassing crucial members in the technology transfer process. However, if appropriate measures are put in place, such issues can be avoided. Indeed, setting up the extended technology transfer project team (see below) should facilitate the overall communication flow.

### The Technology Transfer Process

According to the general perception, technology transfer starts when the contractor and CMO have an agreement to work together and scientific information is transferred. However, in reality, technology transfer starts at the very beginning of this process. During the process of selecting a CMO to perform the contracted work, a limited amount of information must be transferred to allow meaningful dialogue (Figure 3). During this initial period of contact, each party can use the preliminary technology transfer activity to assess the knowledge and experience of each potential partner. The success (or otherwise) of these first technology transfer steps can be highly influential in the ultimate choice of the CMO by the drug discoverer, or alternatively be used by the CMO to make a decision about whether the proposed project fits into the general business development

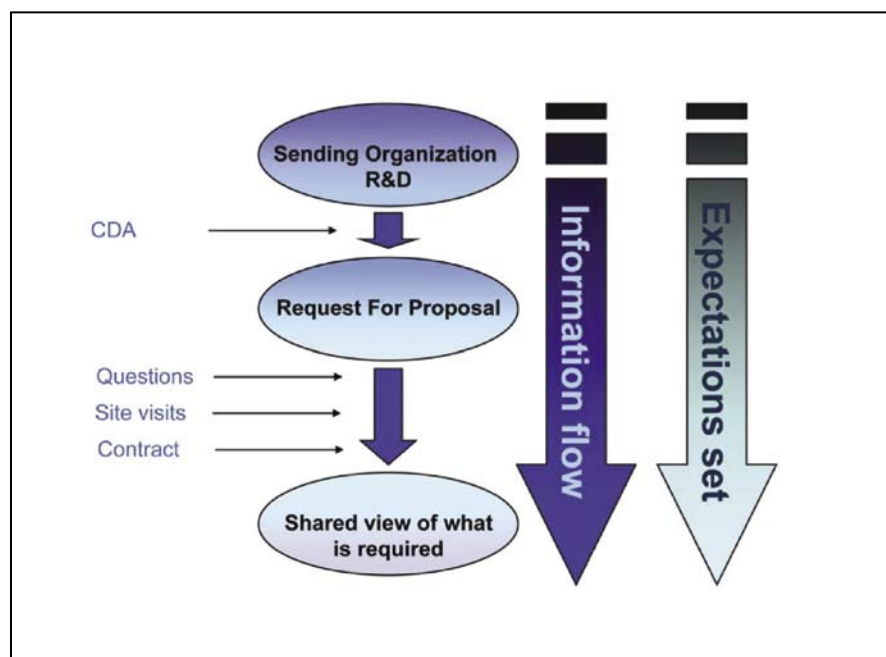


Figure 3. Schematic Diagram Demonstrating Initial Contact Leading to RFP.

strategy.

One of the very first actions in any technology transfer exercise should be the drawing up of a non-disclosure agreement or confidential disclosure agreement (CDA) document. Such documents provide legal protection for all parties in the discussion, protecting their respective intellectual property and procedures. Moreover, this allows freedom of disclosure without fear of compromising sensitive commercial information, and consequently should facilitate the openness between the parties which is necessary for effective technology transfer to occur.

Once an organization selects the CMO for the proposed project, and the CMO accepts the proposal, the technology transfer process can start in earnest. Because the relationship between the drug discovery organization and the CMO is potentially fraught with many pitfalls, several obstacles need to be overcome before the two organizations can start to interact in a meaningful way. These obstacles can be of a business, legal, or technological nature.

It is advisable that the drug discovery organization define its own strategy prior to starting the technology transfer process. This may seem self-evident, but drug discovery companies often have more than one potential new biopharmaceutical product in their pipelines. Therefore, there can be uncertainty regarding which biological product candidate to take forward. Confusion in the basic strategy will result in confusion in the technology transfer process.

## RFP and the Initiation of the Technology Transfer Process

Provided that the business relationship has progressed beyond the initial contact stage, the technology transfer process starts in earnest with the Request for Proposal (RFP) (Figure 4). The RFP should define the scope of the planned project and represents the true start point for knowledge flow between the parties. Moreover, there is flexibility with the RFP process because it is outside of 'formal' roles and responsibilities (*i.e.*, before technology transfer for-

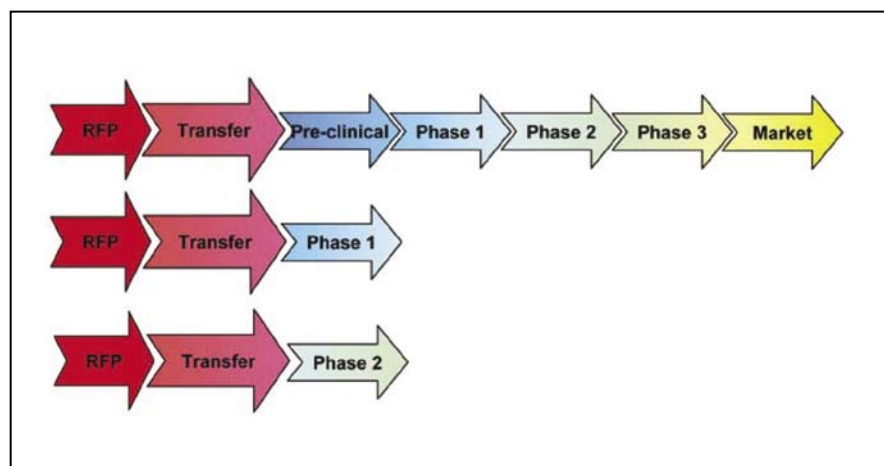


Figure 4. Schematic Diagram Positioning Role of RFP and Technology Transfer in the Relationship of Drug Discoverer and CMO.

mally begins). One function of the RFP is to provide a 'trigger' for questions between the contracting organization and the CMO. The type of questions asked can indicate competency, demonstrating to each party the strengths and weaknesses in their understanding of biopharmaceutical process development and issues that may arise. This is important because the RFP sets expectations for both sending and receiving organizations; expectations that can be difficult to alter once the project has been officially agreed upon and begun. Often problems that arise in process development work can be traced to a misunderstanding at this stage.

The RFP should contain as much information as possible, including:

- General
  - Product type
  - Indication
  - Product development timelines
  - Product information
  - Scale of manufacture/quantity required
  - Physico-chemical properties
  - Solubility, pI, molecular weight, etc.
- Project Scope
  - Define expectations
  - Current status of process
  - Development targets and rationale
  - Quality standards
  - Qualification/validation needs

- Timelines
- Deliverables: reports, material, etc.
- Previous run data (batch manufacturing records [BMRs])
- Manufacture summary reports

For more details see Table 1. Along with a list of what *will* be provided, it can often be useful to state what *will not* be provided, or even what is not required.

## Management of Technology Transfer and The Project Team

Once the RFP has been drawn up and agreed to by all parties, the technology transfer process can formally begin. To effectively manage the technology transfer process, project management principles and associated tools should be employed. A single project team encompassing both parties should be set up. This team can comprise two sub-project teams: one from the contracting organization and one from the CMO. However, there are several types of technology transfer, depending on the stage of process/clinical development, and the magnitude of activity and size of the project team should be adjusted to reflect the project, the customer's needs, and resource levels.

The makeup of the technology transfer project team is also important. Project managers on both sides should be chosen on the basis of experience, aptitude, and skills rather than job title/seniority.

With the formation of the team it is important that a joint 'kick-off' meeting be organised. This meeting should be 'face to face' to foster improved communications between the two parties. Even in the age of rapid telecommunications, with video-conferencing and teleconferences, effective team relationships are best generated by direct person-to-person contact. There is no substitute for personally meeting your counterparts in the collaborating organization.

Within the team, it is important that the roles and responsibilities are understood. At project initiation, a 'RACI' chart or matrix should be agreed upon between contractor and CMO:

- R: responsible for carrying out the work/task
- A: accountable for ensuing work/task completed
- C: need to be consulted prior to decision making
- I: need to be informed

The institution of such a matrix clearly identifies the boundaries of responsibility between individuals and

teams, and helps to prevent duplication of effort.

Having been established, a function of the project team is to define the project plan. This should include:

- Define objectives and deliverables of the technology transfer project
- State constraints/boundaries (e.g., quality standards)
- Agree on timescales and milestones
- Define resources for both contractor and CMO
- Establish communication links
- Agree on basic assumptions
- Agree on the scale of transfer: demonstration of know-how transfer
- Document risks and state mitigation strategies
- Identify criteria for successful technology transfer

- Produce a failure strategy with agreed-upon escalation mechanisms

To ensure that the plan is comprehensive and functionally interrelated, the team should represent all the relevant functions of the project. All functional streams should define detailed plans for their area of responsibility. Included within the technology transfer project team should be the quality function to provide formal sign-off for regulatory reasons. Moreover, any steps that require sign-off/acceptance should be done via joint sign-off by both project sub-teams. This ensures buy-in from both teams and avoids possible future recriminations from issues that might arise.

With the ramping up of the flow of detailed process information, there is an onus on the contracting company to ensure that their documentation is complete. For example, documents such as standard operating procedures (SOPs) and R&D reports need to be sufficiently detailed to ensure that all necessary data are transferred. The omission of vital pieces of information (for example, information in experimental laboratory notebooks) can result in hours of wasted work, which ultimately results in increased costs. Contractors should also safeguard against the loss of crucial scientists on their team. As equally damaging as omitted data is the knowledge lost when a scientist leaves the project. Such information needs to be captured in appropriate process reports, along with a robust data trail.

## Demonstration of Technology Transfer

With all the varied activities associated with technology transfer, it is easy to lose sight of the ultimate goal of the project. Hence, a crucial milestone of the project must be a successful demonstration of technology transfer. The demonstration can vary depending on the requirements of the contractor. This in turn depends on how risk averse the contractor wants to be, as well as financial considerations. It also depends on the state of process

**Table 1. RFP: Typical Process Information.**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• <b>Cell culture/fermentation</b> <ul style="list-style-type: none"> <li>- Cell banks available</li> <li>- Seed expansion</li> <li>- Current bioreactor process scale</li> <li>- OTR</li> <li>- Biomass levels (dry weight: OD relationship)</li> <li>- Development history</li> <li>- Indication of reproducibility</li> <li>- Use of antibiotics/animal derived materials</li> <li>- Any hazardous materials used</li> <li>- Product partitioning</li> <li>- Recovery/clarification procedure</li> <li>- If IB's: solubilisation/refolding</li> <li>- Have viral reduction/removal steps been incorporated</li> </ul> </li> <li>• <b>Downstream</b> <ul style="list-style-type: none"> <li>- Resins/data on binding capacity</li> <li>- Column dimensions/flow rates</li> <li>- Column 'run' conditions</li> <li>- Typical recoveries across steps</li> <li>- Membranes: area and type</li> <li>- Key buffers</li> <li>- Any solvents/hazardous chemicals</li> <li>- Cleaning: any evidence of difficulty of removal</li> <li>- Virus removal/reduction steps</li> <li>- Development history</li> <li>- Indication of reproducibility</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• <b>Analytical</b> <ul style="list-style-type: none"> <li>- Current methods</li> <li>- What will be transferred</li> <li>- What requires development</li> <li>- Development history</li> <li>- Qualification status/needs</li> <li>- IPC tests</li> <li>- Product Specification: expectations</li> </ul> </li> <li>• <b>Formulation/stability</b> <ul style="list-style-type: none"> <li>- Status</li> <li>- Formulation development history</li> <li>- API/Intermediates stability</li> <li>- Regulatory status</li> </ul> </li> <li>• <b>Qualification/validation</b> <ul style="list-style-type: none"> <li>- Cell bank testing</li> <li>- Viral clearance</li> <li>- Analytical</li> <li>- Process</li> </ul> </li> <li>• <b>Process Flow Diagrams</b> <ul style="list-style-type: none"> <li>- Process volumes</li> <li>- Equipment description</li> <li>- % yield across steps</li> <li>- Hold steps and conditions</li> <li>- Processing times</li> <li>- IPC points</li> <li>- Operating parameters and ranges</li> <li>- Are 'ranges' based on data or 'wish/wants'?</li> </ul> </li> </ul> |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

development.

Dependent on the complexity of the process/technology used, and how well it has been established at scale, technology transfer demonstration can occur by transferring straight into the CMO's plant. Even with this direct approach, it is sensible to have one or more laboratory scale or demonstration runs before a full GMP manufacturing run is attempted. The demonstration runs can be performed outside the GMP envelope to reduce costs. However, it is recommended that demonstration runs be performed to GMP to test these procedures.

Nevertheless, even for well-established processes, technology transfer rarely occurs without some unforeseen hitch. Therefore, the recommended and most risk averse approach is to demonstrate successful technology transfer gradually. This approach also reduces the risk of confusing process issues with potential equipment or scale-up issues.

Laboratory scale runs can be performed to establish the process (*i.e.*, to test the logistics and operability). Moreover, a step-by-step approach can be used to separately evaluate each stage, and scale-up/equipment issues can thus be identified or predicted. Laboratory scale runs also have the advantage of familiarising the CMO scientists with the process being transferred, thereby establishing confidence in the process. Associated analytical techniques for in-process testing and drug substance release can also be tested as part of the overall technology transfer process. Laboratory scale runs can be performed either in general or pilot-scale laboratories outside of the GMP envelope. The resulting reduction in scale and operation significantly reduces cost.

It should be recognized that this is an exercise to demonstrate successful technology transfer which should never be combined with process development. Efforts to introduce changes should be resisted. Any required process development can be performed once the process has been successfully established. One exception to this is when a process is

being transferred into the GMP plant during a scale-up technology transfer. Under such circumstances, specific modifications may be required to make the process fit.

As part of the technology transfer demonstration run, a protocol containing the acceptance criteria for the run must be established. Such criteria should include key process parameters, if these have been identified, as well as the acceptance values for the drug substance release specification. Obviously, the acceptance criteria will be dependent on the state of the process prior to the technology transfer, and will be less exacting for a pre-clinical product candidate as compared with an established process. The purpose of the acceptance criteria is to demonstrate that the process functions as defined in the 'technology transfer definition' and produces the 'correct' drug substance with the expected yield and quality.

A technology transfer covers more than the process parameters and final drug substance. Health, safety, and environmental issues should also be addressed, including compliant waste disposal. Procedures should be put in place for safe operation of the process, both in the laboratory and in the plant. Additionally, regulatory compliance should be demonstrated for specifications, analytical methods, and the agreed upon manufacturing process. Where applicable, qualification and validation of analytical assays should also be confirmed.

Last but not least, the whole technology transfer should be performed so that the data is recorded in a contemporaneous manner with an easy-to-follow data trail in place. The exercise should be able to stand up to audit scrutiny, whether by the customer or by the regulatory authorities.

## Summary

Within the scope of this article, technology transfer is regarded as the transfer of knowledge, experience, know-how, reagents, and equipment, and becomes

the interface between the contractor and the CMO. Because pharmaceutical companies are increasingly contracting out process development and manufacture of biopharmaceuticals, it is essential that technology transfer maximises the effectiveness of the transfer and minimises the overall costs. The one over-riding principle of technology transfer is *communication*. Technology transfer should involve two-way communication between organizations and between teams within those organizations. Yet ultimately it's effectiveness relies on 'person to person' communication. Therefore, systems need to be in place to maximise the interaction between the two participants/teams.

It should also be recognized that technology transfer starts with the initial contact between contractor and CMO. A minimal amount of information must be transferred to allow meaningful discussions, irrespective of whether this ultimately results in a working arrangement. If such initial contact is successful, the next stage is to produce the RFP, which should define the project in detail and start the technology transfer process in earnest.

The actual act of technology transfer is performed by the technology transfer team, which is comprised of subteams from both the contractor and the CMO. This team, which involves representatives from all the relevant functions, applies project management principles to the plan and successfully carries out the technology transfer project. Finally the successful technology transfer must be demonstrated by performing the process, either in the plant or at an appropriate scale within the laboratory according to predefined acceptance criteria. By applying the principles described above, technology transfer can be a cost-effective process leading to further process development and manufacture.

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