Excellence in Biopharmaceutical Process Transfer

Boehringer Ingelheim (BI) operates four manufacturing sites across the world: One microbial site in Vienna and three mammalian sites in Shanghai (China), Fremont (USA) and Biberach (Germany) respectively. An additional mammalian facility in Vienna will be operational from 2020 for commercial supply.

Our Biberach site in Germany features Europe's largest biopharmaceutical plant for the manufacture of therapeutic proteins and antibodies from mammalian cell cultures. Here, we operate two large-scale manufacturing plants with six 15 kL bioreactor volumes each (see figure 1 below).

![Boehringer Ingelheim biopharmaceutical manufacturing plants in Biberach, Germany](image)

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In Fremont, we have three 15 kL and two 2 kL bioreactors. The Shanghai plant operates with disposable technology and currently has two 2 kL train for global clinical supply. Naturally, all commercial Boehringer Ingelheim production facilities are certified by the major regulatory authorities (FDA, EMA and MLHW).

**Biopharmaceutical process transfer with Boehringer Ingelheim**

Working in global and multidisciplinary teams, our experienced staff facilitates the technical transfer from our customers directly to the commercial plant. With a track record of countless successful transfers, Boehringer Ingelheim reliably secures the supply to our customers for the benefit of patients worldwide. To give insight into this process, this whitepaper describes and details the interaction and collaboration with customers during the process transfer of late-stage products to one of Boehringer Ingelheim’s commercial manufacturing sites.

**3-Step-Process on the path to large-scale manufacturing**

Once a project has been handed over from the business functions (e.g. Business Development, Key Account Manager) to project management and the project team, first steps are jointly agreed upon by the customer and Boehringer Ingelheim during the project kick-off. Ideally the project kick-off is performed face-to-face and at the manufacturing location of the donor site. The following initial transfer phase sets the stage for an efficient transfer project and can be clustered in three main steps (see figure 2 below).

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**Fig. 2: Biopharmaceutical transfer projects begin with 3-step-process**
The first step is the exchange of information and should ultimately generate a common understanding of the process. Document requirements are outlined by Boehringer Ingelheim and provided by the customer. Usually, first questions are addressed in a first series of teleconferences. Finally, a face-to-face meeting is scheduled, preferably at the customer site, where experts from both project teams can go through the process step by step, either jointly or in breakout sessions. Shipment of the Working Cell Bank (WCB) and the necessary raw materials (cell culture media) is scheduled in this phase.

Necessary facility modifications and large-scale equipment with extensive delivery time are usually identified, discussed and decided in this phase to allow timely ordering, installation and qualification of process-specific equipment.

The second step comprises the preparation of small-scale studies to gather first practical process experience at Boehringer Ingelheim, typically in a 3 L bioreactor scale. This is accompanied by drafting the site-specific process description of the large-scale process. The 3 L scale runs are usually performed in a small Design of Experiment (DoE) setting to check for the most critical upscale parameters (e.g. gassing, agitation). These runs are usually harvested with a generic small-scale method and only partially purified to enable a rough product quality assessment. At the end of this step, the results of the small-scale activities are compared to small-scale data from the partner and discussed with the partner, ideally in a face-to-face meeting.

The third step is the preparation and ‘go’ decision for the large-scale run(s). Two 80 L runs are usually performed to support the transfer. The 80 L confirmation runs have the purpose of confirming the complete upstream and downstream, including a representative harvest step, and enable the complete product quality analysis. During a face-to-face meeting, the final setting can be discussed and, if jointly agreed, the process description can be approved / signed.

Supportive activities are performed in other functional areas and checked regularly in the project team meetings to ensure a timely manufacturing readiness. The project teams are responsible for managing the complex sequence of tasks to avoid lag times e.g. by waiting on certain documents or information.
Key elements to ensure transfer excellence

In the many transfers from customers to our facilities, a number of elements critical to a successful transfer have become evident. Taking these aspects into consideration during the initial phase of a transfer and reflecting on them in the transfer plan substantially increases the probability of success. The following sections will detail the most important of these elements:

- Joint Project Teams and Governance Structures
- Roles and Responsibilities
- Document Exchange in Advance
- Gap / Risk Analysis and Mitigation
- Project Management: Timelines and Milestones
- Lessons Learned
Joint Project Teams and Governance Structures

In Boehringer Ingelheim’s project teams, each key functional area (e.g. Upstream manufacturing (USP), Downstream manufacturing (DSP), Quality Assurance (QA), Quality Control (QC), Supply Chain management (SCM), Regulatory Affairs (DRA)) nominates a team member for the joint project team (JPT). This team member might also act as an internal sub-team lead for their individual discipline. Ideally, the customer matches our team set-up one-to-one. Both teams act as a joint project team during the transfer phase (see figure below). Project managers (PM) on both sides plan and monitor the transfer activities in their respective internal project team and the joint project team. They are also responsible for the communication and escalation of project-related topics in their own organization.

The recommended meeting frequency for joint project teams is bi-weekly. Sub-team meetings - internal or between customer and Boehringer Ingelheim - are usually scheduled as needed.

The governance structure ensures a clear advisory and decision process, where the joint project team can recommend certain options at pre-defined milestones or can escalate topics and request a decision where needed (see figure 5 below).
The Joint Steering Committee meets at the defined milestones, usually once or twice a year or if requested by the JPT. It is typically represented by the Director Level of the key functional areas and responsible for project-specific decisions.

Senior management is involved in the Executive Steering Committee, typically represented by the VP- or Senior VP-level. Meetings are scheduled as needed or at important milestones. Topics in the ESC are typically strategic decisions or decisions influencing the complete project portfolio with this customer. This set-up ensures secure and rapid data exchange, empowered teams, fast solutions, aligned decision-making and (high level) management involvement where necessary.

**Roles & Responsibilities**

It is also quite important to jointly agree on roles and responsibilities for the individual tasks during the transfer process. This becomes even more vital when dealing with more than two parties involved in a transfer project. Boehringer Ingelheim offers various tools.
to organize and track the multiple tasks during a transfer project, but we are always open to using tools provided by the customer.

**Document exchange in advance**

For a successful transfer, all the relevant documents need to be exchanged before the kick-off meeting or at the very beginning of the transfer phase at the latest. The teams need to review the documents and prepare themselves in order to implement the individual work packages. Typically, the customer has provided some (basic) information to allow Boehringer Ingelheim to compile a proposal as a starting point for the evaluation and negotiation phase. However, this information is less detailed and therefore not sufficient to understand the process as it is currently developed and implemented at the donor site for a successful transfer. The Boehringer Ingelheim team in particular needs to gain an in-depth understanding of the process and of all the other related topics to perform a detailed facility fit, identify and discuss potential gaps (see chapter Gap Analysis) and compile a Boehringer Ingelheim plant-specific process description. For example, the following documents are typically requested from the customer:

- Product MSDS, product type, daily dose, solubility, toxicity
- Detailed process description per unit operation, including a parameter list of all process parameters with NOR & PAR ranges
- Most current Executed Batch records for all Up- and Downstream steps
- Online and offline process data (e.g. gassing profile, cell growth, chromatograms, conductivity/UV)
- Step yields and overall process yield from harvest until BDS
- List of buffer and media solutions and volumes, with composition/concentration of components identified
- Overall bill of material (BOM) – incl. Vendor and Incoming Release Specifications
Leachable/Extractable assessment and study on removal of biologically active substances (Viral Clearance Validation report)

Process Validation Reports

WCB COAs, characterization reports and BSE/TSE statement, technical report on the stability of the cell line

Equipment geometry and operation mode of customers’ bioreactors (power input of stirrers of all bioreactors, kinds of blades, gassing strategy)

Analytical method descriptions (SOP), validation protocols / reports

Current version of in-process control, release and stability specifications

Not all the requested documents may be available at the customer site due to the maturity of the process, i.e. the current (clinical) phase of the process / product. It is then the task of the mutual project team to collect and compile the missing data to support the transfer.

Gap / Risk Analysis and Mitigation

Another important step during the process transfer is the gap or risk analysis. This should not only focus on process differences between both sites, but also on procedures within manufacturing. Technical reports from the customer site reflect the process as implemented there, using equipment and systems available at the donor site. However, this will never be completely identical to the Boehringer Ingelheim setup. Once the manufacturing process is established at the Boehringer Ingelheim site, there will be a need to re-evaluate ranges, set points or procedures. The joint project team needs to address and agree to these changes to support the site-specific process description and ranges, and to validate the future process to manufacture commercial batches.
Each joint functional team should go through the process together and identify any necessary adaptations or procedures diverging from the original process at the customer site. The individual topics can be listed and rated according to a risk evaluation matrix (example see figure above). No risk mitigation is needed for lower risks. Contingency plans with trigger points are evaluated for medium risks. For higher risks, actions are taken to modify topics in order to eliminate risks or reduce their probability or severity.

**Project Management: Timelines & Milestones**

In addition to the aspects mentioned above, it is essential to have not only a common understanding of the initial phase of the process transfer, but also a complete overview of the project. Slight delays of individual sub-tasks within a high-level work package can significantly impact the overall timeline due to many cross-linked and staggered activities. The project manager, together with the sub-team leaders, should be aware of these pitfalls and have regular updates on the timeline and how to deal with modifications.
Milestones should be implemented to review the teamwork and progress of the project prior to entering the next phase. Usually, since work packages are staggered and timelines are under pressure, there will not be enough time to finalize one phase completely before starting the upcoming one. However, before critical activities are initiated (e.g. thaw for engineering run(s) or validation runs) a joint team review at a face-to-face meeting with steering committee involvement should be scheduled.

**Lessons Learned: Transferring biopharmaceutical projects**

The key to our success with project transfers is our drive for continuous improvement. That is the motivation to conclude any project with a session on ‘lessons learned’ The purpose of such a session is to identify recurring patterns and give insight into what worked well and what may be further improved. All team members from both sides may greatly benefit from these insights and take them back into their respective organizations, making each transfer even smoother than the last. Some pitfalls that have been identified in the past include:

- Analytical method transfer is underestimated and initiated too late. There are also many documents which one might consider summarizing in a kind of method description (comparable to a process description).
• Many documents with similar and comparable content are compiled. It should be tried to reduce them.

• Project management needs to take an active role in document tracking and oversight. Review cycles, approval and translation should be defined early in a Quality Agreement, not only for batch records but also for CMC dossier documents.

• Source data review takes time and expends resources.

• Share knowledge by having a person in the plant during the initial runs, at least during the most critical activities, to address any emerging issues in a timely manner.

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